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ACUTE SWELLING OF OLIGODENDROGLIA

A SPECIFIC TYPE OF NEUROGLIA CHANGE *

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The introduction of a cytologic method which throws new light on anatomic structure is often the preliminary step toward a further knowledge of pathologic changes. Del Rio-Hortega's description of oligodendroglia [1] by the use of his silver carbonate method has made possible the following study which shows that these cells undergo a specific alteration which is often the only evidence of a pathologic process in the central nervous system.

CLASSIFICATION OF THE INTERSTITIAL CELLS

Under the heading of interstitial cells are included neuroglia and microglia cells.

The most concise and complete modern description of neuroglia astrocytes is to be found in a publication by Cajal [2] in 1913. Much of this description was, of course, not new but the gold chloride method which he devised led him to certain definite conclusions. He gave a clearer picture of the fibrous astrocytes of the white matter and the protoplasmic astrocytes of the gray substance. He showed that there are mixed cells, especially in the dog, which are part fibrous and part protoplasmic. These two types have a common ectodermal origin and

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* Read at the Fifty-First Annual Meeting of the American Neurological Association, Washington, D. C., May, 1925, through the courtesy of Dr. Louis Casamajor.

* From the Departments of Surgery and Pathology of Columbia University in the Presbyterian Hospital.

1. Del Rio-Hortega, P.: Estudios sobre la neuroglia; la glia de escasas radiaciones (oligodendroglia), Bol. d. la Real Soc. Españ. d. Historia Natural **10**, (Jan.) 1921.

2. Cajal, S. Ramón y: Contribución al conocimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. **11**:255-315, 1913.

under abnormal conditions they may lose the characteristics that differentiate them from each other and undergo rapid amitotic division. Cajal showed that every astrocyte has one or more vascular attachments. He took the attitude that neuroglia fibers are never emancipated from the cell body as maintained by Weigert and cast much doubt on Held's neuroglia syncytium.

The clarity of Cajal's description made it evident that the large group of so-called small cells or "neuroglia without expansions" differed radically in structure and behavior from astrocytes. He called them the third element of the central nervous system.

Del Rio-Hortega, using silver carbonate as a stain, found that these so-called "neuroglia cells without expansions" do actually possess expansions. The more numerous of these cells he named oligodendroglia or glia with few expansions. They appear in large numbers, often in rows in the white matter, but they also form most of the perineuronal satellites. As they, like astrocytes, evidently develop from ectoderm, it seems best to consider them one form of neuroglia. They differ from astrocytes in that they never contain fibers and never possess vascular footplates. They resemble astrocytes in that they have nuclei similar in chromatic content though somewhat smaller and more apt to be round. Both types of cell have a centrosome and polar Golgi apparatus which resembles that seen in cells of secreting glands. Both astrocytes and oligodendroglia contain gliosomes which may be simultaneously stained and which are identical in appearance.

In addition to oligodendroglia, Del Rio-Hortega pointed out another group of cells whose expansions had not been previously stained. These are microglia [3] which appear to be of mesodermal origin. They act as phagocytes in destructive processes [4] in the central nervous system and are present everywhere though more numerous in the gray substance where they form a minority of the perineuronal satellites.

Therefore the interstitial cells of the central nervous system may be divided into neuroglia and microglia. The neuroglia is made up of astrocytes and oligodendroglia. The astrocytes appear usually as protoplasmic in the gray, and fibrous in the white matter. Oligodendroglia has much the same form in either part of the brain, but in the gray provides the majority of perineuronal satellites, and in the white, the interfascicular glia.

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3. Del Rio-Hortega, P.: El "tercer elemento" de los centros nerviosos; histogénesis y evolución normal: éxodo y distribúción regional de la microglia, Mem. de la Real Soc. Españ. de Historia Natural **10**:213-268, 1921.

4. Penfield, Wilder: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77-89 (Jan.) 1925.

Changes undergone by neuroglia astrocytes in pathologic conditions are familiar to all neurologists, as are also the pathologic forms of microglia; i. e., rod cells and compound granular corpuscles. But for oligodendroglia, except for the possibility that they may give rise to certain tumors, as suggested by Cushing and Bailey,[5] no pathologic change has previously been described.

AMEBOID GLIA AND CLASMATODENDROSIS

Alzheimer[6] described in certain acute conditions of the central nervous system the change of neuroglia astrocytes into forms which, he said, resembled amebas. He therefore called them ameboid glia because of their appearance, not because he assumed movement. In this change the protoplasmic or fibrous astrocytes swell and the cytoplasm breaks up to form Füllkörperchen or filling bodies. Certain types of granules appear. He likewise pointed out that there was to be seen in the perineuronal satellites a corresponding, but somewhat different, alteration. The cell body appeared round or oval and contained granules similar to those in ameboid glia.

Ziveri[7] urged that the ameboid alteration was a degenerating or cytolitic rather than an active cellular change. The various granules that appeared, he likened to the similar granules in degenerating nerve cells. He believed the cells which played an active rôle in catabolic processes were derived from the third element of Cajal rather than from Alzheimer's ameboid glia. Buscaino[8] showed that the production of ameboid glia could be a perfectly passive process, induced by means

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5. Bailey, P., and Cushing, H.: Investigation into Histogenesis and Histopathology of Gliomas, Including Classification and Correlation of Their Clinical History, read at the meeting of the American Neurological Society, May, 1925.

6. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe, Histol. u. histopath. Arb. ü. die Grosshirnrinde **3**:401-550, 1910. Achúcarro, N.: Neuroglia y elementos intersticialis patológicos del cerebro, impregnados por los metodos de reduccion de la plata ó por sus modificaciones, Trab. d. lab. de invest. biol. **9**:161-179, 1911. Bailey, P., and Hiller, G.: The Interstitial Tissues of the Central Nervous System: A Review, J. Nerv. & Ment. Dis. **59**:337-361, 1924.

7. Ziveri, A.: Alcune considerazioni sulla cosiddetta neuroglia adendritica (tercer elemento di Cajal), Ann. di Nevrol. **6**:3-24, 1914.

8. Buscaino, V.: Sulla genesi e sul significato delle cellule ameboidi, Riv. di patol. nerv. **18**:360-387, 1913. Marinesco, G., and Minea: Die Kultur des Gliagewebes der Grosshirnrinde in vitro; Angaben zur Bildung und Funktion der amöboiden Zellen, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:137, 1925. Urechia, C.: Recherches experimentales sur la transformation amoeboide des cellules névrogliques, Compt. rend. Soc. de Biol. **88**:931-932, 1923. Walter, F.: Untersuchungen über die amoeboide Glia und Clasmatodendrose, Ztschr. f. d. ges. Neurol. u. Psychiat. **66**:232-257, 1921.

of acid intravascular injections or immersion in various solutions. Thus he produced ameboid glia both in vivo and in vitro. The change, he said, depends on the equilibrium between the colloidal constituents of neuroglia and the ambient liquid.

Cajal [2] gave a clear description of a change that occurs post mortem in neuroglia. This autolytic change he called clasmatodendrosis,[9] as the most striking feature is fragmentation of the dendrons or expansions. This change may occur within a few hours of death or may be absent after twenty-four hours. It is also usually scattered irregularly through the central nervous system appearing first, as a rule, in the gray matter.

Del Rio-Hortega [10] pointed out that the ameboid glia of Alzheimer might also be cadaveric in origin and that the fragmentation of neuroglia expansions which Cajal had called clasmatodendrosis, produced the filling bodies or Füllkörperchen, of Alzheimer. He likewise pointed out that the change occurred in a number of acute conditions of the brain and that in areas of softening there appeared a central zone of so-called ameboid glia cells, next to these a layer of fragmented cells, and outermost a ring of neuroglia undergoing active hypertrophy. Thus, in the two inner layers, the change was degenerative; in the outermost layer, constructive.

Rosenthal,[11] in 1913, pointed out that Alzheimer had really described two types of ameboid neuroglia cells. The first appeared chiefly in response to pathologic changes in myelin sheaths and nerve cells. In this type, the neuroglia cells were filled with large fuchsinophil granules. The second type of ameboid glia was loaded with granules staining with methyl blue. This latter type appeared as a direct response to acute disease conditions and degenerated rapidly forming filling bodies. Thus, it may be assumed that the latter change, at any rate, is degenerative. He pointed out that, in addition to the autolytic production of ameboid glia, the same change could be produced experimentally before death by toxic injections of guanidine.

Rosenthal likewise described, under similar abnormal conditions, an earlier change in what he called the small round glia cells or satellite cells (i. e., oligodendroglia). This change, which was characterized by pyknotic shrinking of the nuclei and an increase in cytoplasm which may

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9. Penfield, W., and Cone, W.: Regressive Changes of Neuroglia: A Comparative Study, to be published.

10. Del Rio-Hortega, P.: Sobre la verdadera significación de las células neróglicas llamadas amiboides, Bol. d. la Soc. Españ de Biol. **8**:229-243, 1918-1919; Contribution à l'étude de l'histopathologie de la neuroglie; ses variations dans le ramollissement cérébral, Trab. d. lab. de invest. biol. **14**:1-34, 1916.

11. Rosenthal, S.: Experimentelle Studien über amöboide Umwandlung der Neuroglia, Histol. u. histopath. Arb. ü. die Grosshirnrinde **6**:89-160, 1913.

be vacuolated, he called preameboid change. He believed these preameboid cells might either revert to normal, or continue their change to form ameboid glia.

ACUTE SWELLING OF OLIGODENDROGLIA

By means of Rio-Hortega's silver carbonate technic, somewhat modified,[12] we have been able to show that the changes vaguely seen by Rosenthal constitute a specific reaction of oligodendroglia with clear-cut transitions. The swollen cells thus produced are, however, not preameboid, as he thought. They do not develop into ameboid glia.

The change is characterized by hypertrophy of the cytoplasm, followed by swelling and vacuolization of the cell body which may progress to the point of extrusion of the nucleus in extreme cases. As the change appears to be acute, it has seemed well to call the process acute swelling of oligodendroglia.

As seen in figure 11, the earliest change from the normal (*A*) seems to be an irregular increase in perinuclear cytoplasm (*B*); granules stand out clearly and the protoplasm uniting the granules of the expansions ceases to stain, leaving granular chains.

Next, swelling of the cell body begins. Unstained fluid pushes out the cell membrane (*C* and *D*, fig. 11)and granules are seen on the surface of this membrane and on the septa or "protoplasmic girders" which divide the cell body into vacuoles. The expansions decrease in number but are represented by chains of granules. Finally, in extreme cases the cell membrane ruptures or disappears and the nucleus appears naked (*G* and *H*, fig. 11).

The nuclei themselves vary a good deal in different phases of the change, staining with greater or less intensity, but in general there is a progressive shrinking and pyknosis of the nucleus.

Acute swelling has been studied in thirty cases and in experiments, an outline of which follows:

REPORT OF CLINICAL CASES

CASE 1.—*Tuberculous Meningitis.*

History.—A. D. was admitted to the Presbyterian Hospital, Oct. 28, 1924, with the complaint of two weeks of vomiting, loss of weight, increasing apathy and convulsions.

Physical Examination.—The infant was well nourished and stuporous. There was inconstant strabismus. The pupils were round and equal and reacted sluggishly to light. The neck was stiff, the legs were somewhat spastic and Kernig's sign was positive.

12. Penfield, W.: Oligodendroglia and Its Relation to Classical Neuroglia, Brain **47**:430-452 (Dec.) 1924; it was found that better results were obtained at times by fixation of only a few hours in ammonium-bromide-formaldehyde solution after intracarotid injection of the same fixative.

The spinal fluid contained 180 cells per cubic millimeter, most of which were lymphocytes. On standing, a web formed in it and in the web tubercle bacilli were found.

Course.—The patient's condition steadily failed. There were daily convulsions and increasing stupor, with death on the eighth day after admission. The clinical diagnosis was tuberculous meningitis.

Necropsy.—(Performed two hours after death.) The necropsy diagnoses were: tuberculosis of the bronchial lymph glands, intestines and leptomeninges; also bronchopneumonia.

Microscopic Findings.—Frozen sections of blocks of the brain stained specifically for oligodendroglia showed an astonishing degree of swelling of these cells in both the white and the gray matter. In the white matter the swollen cells

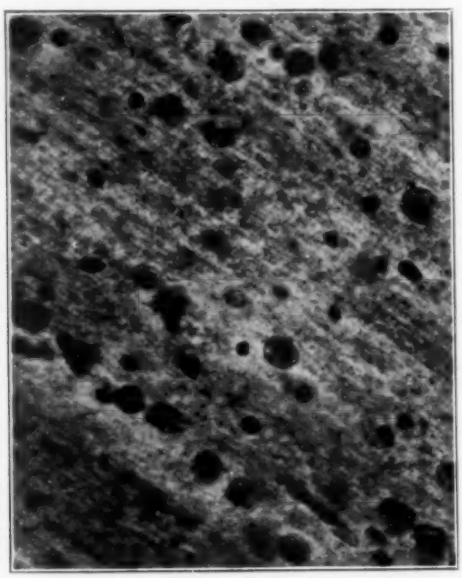

Fig. 1 (case 1).—Tuberculous meningitis: extreme degree of acute swelling of oligodendroglia. Photomicrograph of silver carbonate stain from substantia blanca.

were present in rows between the medullary sheaths (fig. 1) and a few swollen cells were present around the vessels. In the gray matter, oligodendroglia satellites were similarly swollen.

The cell nuclei varied to some extent but were generally a little smaller than normal and pyknotic (fig. 2). The cell bodies were roughly four times as large as the nuclei, and their cytoplasm was lightly granular, containing clear vacuoles. Cytoplasmic expansions had disappeared or were stained very faintly, their outlines being indicated by granules (fig. 2). For the most part cell boundaries were distinct, but occasionally cells were found which seemed to be extruding their nuclei and similar nuclei were found free with no trace of cell.

Cajal's gold sublimate stain for neuroglia astrocytes showed regressive changes in these cells which have been described under the term clasmatodendrosis (fig. 5). Microglia cells stained by Hortega's silver carbonate were found to be normal.

CASE 2.—*Malnutrition.*

History.—D. R., aged 2 months, was admitted to the Presbyterian Hospital, Jan. 4, 1925, because of severe diarrhea and loss of weight. The illness began when the mother's milk failed and the infant was placed on artificial feedings.

Physical Examination.—The patient was apathetic and markedly emaciated. The red blood cell count was 1,300,000 and the hemoglobin was 35 per cent. The white blood count was 38,000 with 75 per cent lymphocytes. *Staphylococcus albus* was grown from the blood.

Course.—The infant was given a blood transfusion on the day of admission and seemed to respond to the new feeding regimen. However, on January 9, after a transfusion, he rapidly became apathetic, his respirations irregular, and his pulse

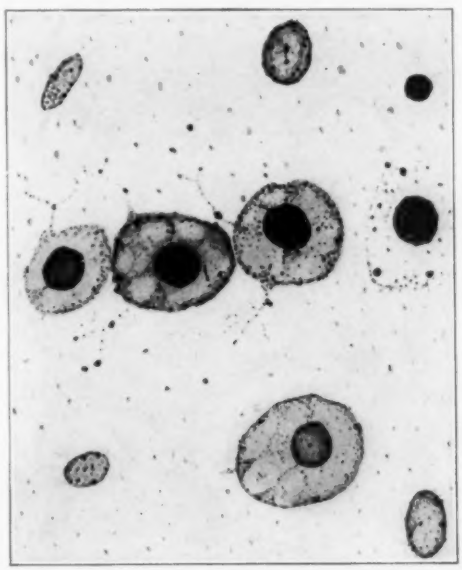

Fig. 2 (case 1).—Tuberculous meningitis: acute swelling of oligodendroglia showing pyknosis of nuclei, vacuolization of cytoplasm, disappearance of expansions and finally disintegration of cells. Silver carbonate stain.

slow and weak, and at the end of twelve hours he died. The clinical diagnosis was malnutrition.

Necropsy.—This was done six and one-half hours post mortem and disclosed an ulcerative colitis, anemia and a small hemorrhage from the longitudinal sinus at the site of the transfusion. Aside from this small hemorrhage the brain showed nothing unusual in the gross.

Microscopic Findings.—The most extreme grade of swelling of oligodendroglia noted in this report was observed in the specifically stained sections from the brain of this patient. In the white matter the oligodendroglia cell cytoplasm was elongated, apparently due to its position between the medullary sheaths. In some cases the greatest diameter of the cell body was five times its nucleus. The cytoplasm was granular and vacuolated as in the preceding case. Indistinct cytoplasmic boundaries were present about some of the cells (fig. 3 *A*) and a few

oligodendroglia nuclei were to be found which had no cytoplasm (fig. 3 *B*). Microglia cells throughout were normal in appearance (fig. 3 *C*).

In sections stained by Cajal's gold method, most of the astrocytes present in both the gray and white matter were normal (fig. 4). There were areas, however, in the deeper layers of the cortex and in the white matter in which clear examples of clasmatodendrosis were present (fig. 5).

CASE 3.—*Primary Sarcoma of the Meninges.*

History.—E. W., aged 54, was admitted to the Presbyterian Hospital, Jan. 31, 1925. The illness began six months previously when he fell, striking his head, and remained unconscious for one minute. From this time he complained of

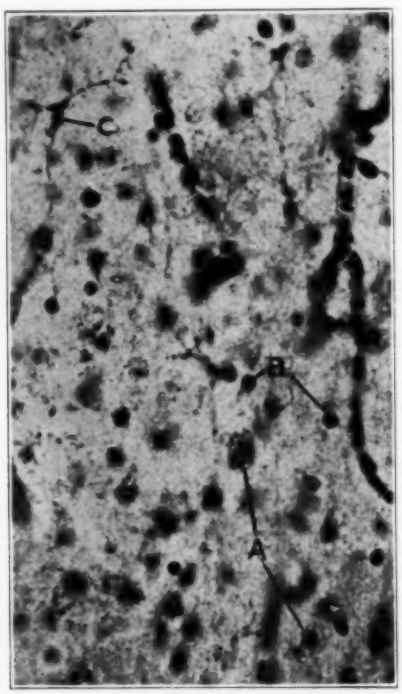

Fig. 3 (case 2).—Malnutrition: acute swelling of oligodendroglia, *A;* free oligodendroglia nuclei, *B*; normal microglia, *C*. Silver carbonate stain.

increasingly severe frontal headaches, his disposition changed, he began to vomit, and though he remained at work, he was drowsy and tired.

Physical Examination.—The patient was completely disoriented. He felt he was going blind. He cooperated well, but was confused. He picked at the bed clothing and imaginary objects. The eye grounds showed a slight papilledema and there was nystagmus on looking to either side. There was left facial weakness. The tendon jerks were slightly more active on the right and there was some muscular weakness on this side. The abdominal and cremasteric reflexes were absent. Plantar stimulation gave a flexor response. Sensation was normal.

The spinal fluid on repeated examination was a clear light yellow with from 20 to 170 cells per cubic millimeter, most of which were lymphocytes. Globulin

varied from one-plus to four-plus, and the sugar content from 0.3 to 0.65 Gm. per liter.

Course.—During the seven weeks in the hospital, the diagnosis varied between encephalitis and pachymeningitis hemorrhagica interna. For a week before death on March 18, the patient was semicomatose.

Necropsy.—This was done forty-five minutes post mortem. It showed a diffuse primary sarcoma of the leptomeninges.

Microscopic Findings.—In all sections there was advanced, acute swelling of oligodendroglia. Microglia was normal in appearance. The neuroglia astrocytes were normal in many areas but in others clasmatodendrosis was present. This

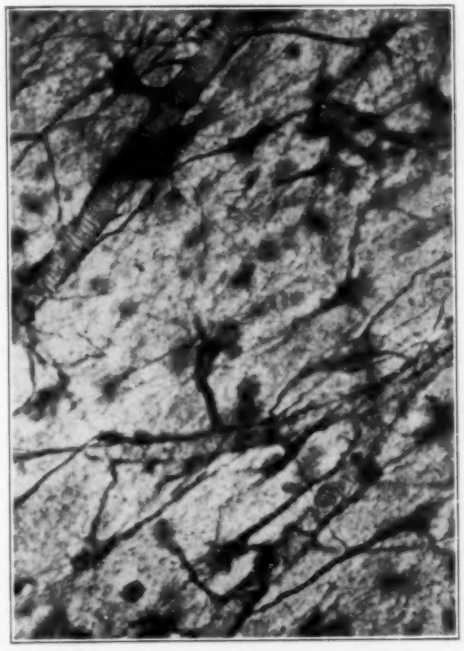

Fig 4 (case 2).—Malnutrition: area showing normal astrocytes with their vascular attachments. Cajal's gold chloride sublimate stain.

patchy distribution of the astrocyte change is not uncommon, as was seen in case 2.

CASE 4.—*Anterior Poliomyelitis.*

History.—J. L., aged 4½ years, a private patient of Dr. Howard Mason, was discovered to have a temperature of 103.6 degrees on the morning of March 13, 1925.

Physical Examination and Course.—The patient presented in the morning only a mild inflammation of the throat. At noon, left internal strabismus appeared. At 6:30 p. m., mucus was present in such large amounts as to cause difficulty with respiration; the left internal strabismus was more marked and there was slight ptosis of the left eyelid and flaccid paralysis of the left side of the face. During the next few hours the paralysis rapidly spread, involving the entire right side and part of the left upper extremity.

Lumbar puncture gave fluid which contained 380 cells per cubic millimeter, 80 per cent of which were lymphocytes. A distinct pellicle formed in the fluid one-half hour after it was drawn. No tubercle bacilli were stained in it. Culture of the fluid was negative.

At 11 : 10 p. m., respiration stopped with no other premonitory signs than those described above.

Necropsy.—This was performed twelve hours postmortem. The usual lesions of an acute extensive anterior poliomyelitis were found.

Microscopic Findings.—Longitudinal sections of the cord, stained specifically, showed rows of swollen oligodendroglia cells (fig. 6), and cross sections demon-

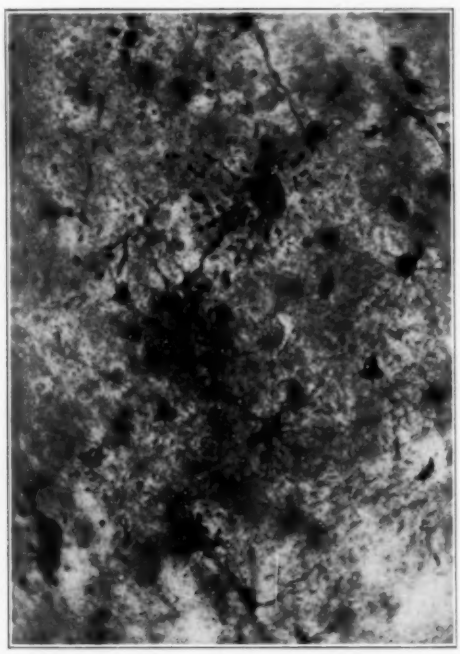

Fig. 5 (case 2).—Malnutrition: area showing clasmatodendrosis marked in some cells and slight in others. Cajal's gold chloride sublimate stain.

strated these cells among the myelin sheaths. Similarly stained sections from the cerebrum showed acute swelling of oligodendroglia in both white and gray matter (fig. 7).

There was some thickening of microglia cell cytoplasm and moderate clasmatodendrosis of neuroglia astrocytes.

CASE 5.—*Cardiac Insufficiency, Stupor.*

History.—Henry M., aged 43, was admitted to the Presbyterian Hospital complaining of shortness of breath and a cough which raised rusty sputum. For the previous four years he had had symptoms of cardiac disease which had increased for six weeks before admission.

Physical Examination.—The patient was moderately dyspneic and cyanotic. There was an area of increased dulness in the right lung. The heart was greatly

enlarged and the heart sounds were irregular. There was a marked pulse deficit at the wrist.

Course.—The patient was admitted at noon and at 7 p. m. he began to show signs of moisture in the right lung. He was stuporous, his pulse was almost imperceptible and the pulse deficit high. Both lungs rapidly filled with moisture and breathing became more and more labored. The patient died nine hours after admission.

Necropsy.—This was performed nine and a quarter hours post mortem. The following were the important findings: chronic valvular disease of rheumatic origin, thrombi in the left auricle, healed infarcts of the kidney and spleen, and syphilis of the pulmonary artery. Aside from edema of the leptomeninges and a

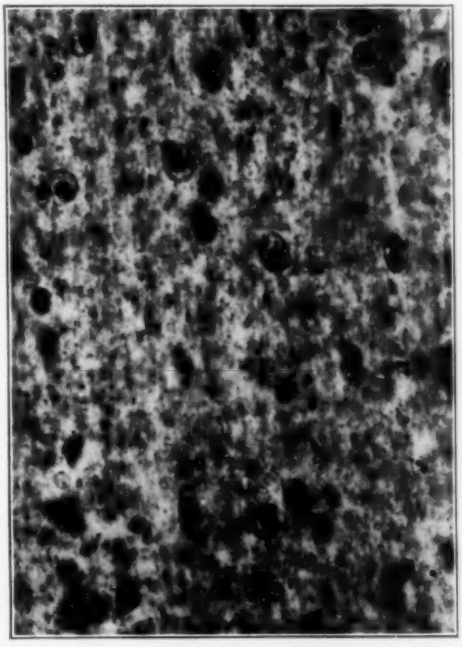

Fig. 6 (case 4).—Anterior poliomyelitis: acute swelling and destruction of oligodendroglia in a longitudinal section of the spinal cord. Silver carbonate stain.

small area of softening in the floor of the lateral ventricle, the central nervous system showed no gross abnormality.

Microscopic Findings.—Here again in all sections stained with silver carbonate, acute oligodendroglia swelling was present to an advanced degree. Microglia cells appeared normal. The neuroglia astrocyte expansions showed some hypertrophy but in certain areas were beginning to break up.

CASE 6.—*Pneumococcus Meningitis.*

History.—M. G., aged 8, was in coma when admitted to St. Mary's Hospital, Feb. 9, 1925. Her illness began two days before admission, when she had felt chilly and nauseated. Headache and vomiting appeared and she became delirious.[13]

13. For permission to study the necropsy material in this case we are indebted to Dr. W. C. Clarke.

Physical Examination.—There was ptosis of the right eyelid and right external strabismus; the right pupil was pinpoint but reacted to light. Plantar responses were extensor on both sides. Brudzinski's sign was positive. There was no opisthotonus.

Lumbar puncture yielded an opalescent fluid which contained 2,508 cells per cubic millimeter, most of which were of polymorphonuclear type. The smear showed gram-positive cocci in pairs and short chains. The organism was identified as the pneumococcus but was not grouped.

Course.—The patient died shortly after admission, having been in coma about five hours.

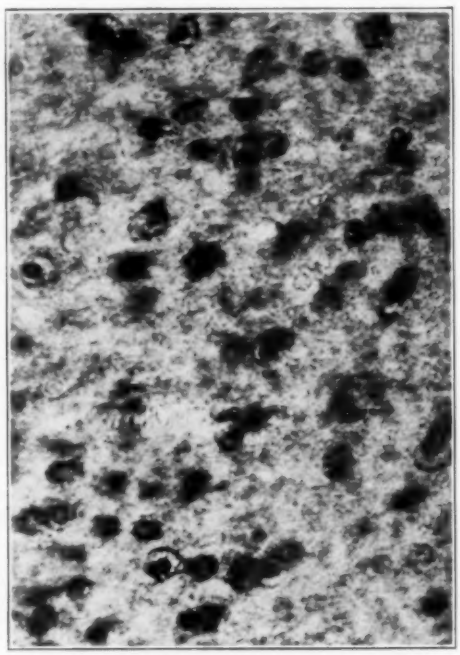

Fig. 7 (case 4).—Anterior poliomyelitis: acute swelling of oligodendroglia in the substantia blanca of the brain. Silver carbonate stain.

Necropsy.—This was done twenty-four hours post mortem, and revealed a purulent pneumococcus meningitis.

Microscopic Findings.—Sections stained for oligodendroglia showed extreme swelling of these cells in both the gray and the white matter. The microglia, which was stained simultaneously, was normal.

CASE 7.—*Hydrocephalus.*

History.—C. N., aged 2 years, was admitted to the hospital Dec. 15, 1924, because of an enlargement of the head.

Physical Examination.—The baby was well nourished. His head was large and the sutures were widely separated. All the deep reflexes were obtainable. There was a positive Babinski sign on the right. He could not walk. The greatest circumference of the head was 57.5 cm.

Course.—After diagnostic ventricular puncture there was great improvement for several weeks; this was followed by an evident exacerbation of the ventricular pressure and death with bronchopneumonia.

Necropsy.—This was done twelve hours post mortem. There was bronchopneumonia in both lungs and an extensive internal hydrocephalus.

Microscopic Findings.—The interfascicular oligodendroglia of the white matter of the brain and cord showed advanced acute swelling. The satellite oligodendroglia of the gray matter presented a similar change. Microglia was normal. Moderate clasmatodendrosis of the astrocytes was present.

CASE 8.—*Carcinoma of the Stomach with Emaciation.*

History.—On Dec. 2, 1924, W. E., aged 54, was admitted to the hospital complaining of pain in the stomach which had been present for one year. She had lost 40 pounds (18 Kg.) in the last year.

Physical Examination.—The patient was emaciated, and at the level of the pylorus a mass could be felt.

Course.—December 5, an exploratory operation was performed. An inoperable carcinoma of the stomach was found and a gastro-enterostomy done. After a smooth postoperative course, the patient gradually weakened. Urinary retention developed and was followed by incontinence. She became practically comatose and died on the twenty-eighth day after the operation.

Necropsy.—This was done seven hours after death and revealed numerous metastases from the carcinoma of the stomach. The brain showed nothing remarkable in the gross.

Microscopic Findings.—Sections disclosed moderate swelling of oligodendroglia in both the gray and the white matter. The microglia appeared to be normal, as were the neuroglia astrocytes.

The following cases have been studied since this communication was read before the American Neurological Society. The details of most of them will be omitted.

CASE 9.—(F. P.).—*Cerebral Embolism.*—This occurred four hours and thirty minutes before death. Necropsy was performed fourteen hours after death. In the area of brain corresponding to the distribution of the blocked vessel there was extreme oligodendroglia swelling and ameboid change of astrocytes. On the other side of the brain the astrocytes were quite normal.

CASE 10.—(D. L.).—*Cerebral Abscess.*—Necropsy was performed two hours after death. Oligodendroglia swelling was intense and clasmatodendrosis was present.

CASE 11.—(H. D.).—*Cerebral Abscess.*—Necropsy was performed five hours after death. Both oligodendroglia swelling and ameboid glia were present.

CASE 12.—(J. J.).—*Cerebral Abscess.*—Necropsy was performed one hour and fifteen minutes after death. Oligodendroglia swelling was extreme and clasmatodendrosis present.

CASE 13.—(B. T.).—*Myxedema.*—Death was sudden and unexplained after a few hours of stupor. Necropsy was performed four hours after death. Acute swelling of the oligodendroglia was present but astrocytes were normal.

CASE 14.—(D. R.).—*Chloroleukosarcoma.*—Necropsy was performed six hours post mortem. Acute swelling of the oligodendroglia was present but the astrocytes were normal.

CASE 15.—(J.).—Normal oligodendroglia was found in a case of traumatic death. The patient was an able-bodied man who fell while at work, receiving a fractured skull. He reached the Presbyterian Hospital within twenty minutes after the accident, in an unconscious condition. Blood and pieces of brain of rather surprising size were found coming from his ear. This cerebral tissue was examined. The oligodendroglia and astrocytes were quite normal in every way.

NORMAL OLIGODENDROGLIA FROM OPERATIVE CASES

CASE 16.—(P. R.).—*Probable Tumor of Brain.*—Cerebral tissue was removed at operation by Dr. Charles Elsberg with an exploratory hollow needle. No swelling of oligodendroglia and no ameboid glia were found.

CASE 17.—(B. B.).—*Probable Tumor of Brain.*—The cerebral tissue was obtained at operation by Dr. Charles Elsberg, as in case 16. Oligodendroglia and astrocytes appeared quite normal.

CASE 18.—(H.).—*Probable Tumor of Brain.*—The cerebral tissue was obtained at operation by Dr. Charles Elsberg as in case 16. No acute swelling of oligodendroglia and no ameboid glia were found.

CASE 19.—(C. F.).—*Glioma of the Right Cerebral Hemisphere.*—Cerebral tissue was removed with a hollow exploratory needle. Both oligodendroglia and astrocytes were normal. In this case and in cases 16, 17 and 18 papilledema was present and the neuroglia was normal.

CASE 20.—(K. H.).—*Cerebral Embolus.*—Cerebral tissue was obtained at operation with a hollow exploratory needle from the side of the lesion. Exploration was made because of a suspicion before operation of the presence of brain abscess, which proved unfounded. Marked acute swelling of oligodendroglia and ameboid change in astrocytes were present.

CASE 21.—*Severe Epilepsy.*

History.—C. M., a girl, aged 15, under the care of Dr. H. R. Geyelin, had had a convulsion every week or two. There was an aura of discomfort in the right side of the abdomen and the convulsive movements were chiefly, though not exclusively, of the right side. For three weeks before operation, the convulsions became much more frequent, occurring up to thirty times a day. They were not controlled by any of the usual sedatives nor by starvation. The patient was clear mentally but slept a great deal. There was no papilledema and the deep reflexes were practically normal.

Operation.—A conservative type of exploratory operation was undertaken. Trephine openings were made over the left parietal and occipital lobes, and from these points exploratory punctures of the brain were made and specimens of cerebral tissue withdrawn in hollow needles and immediately fixed. The brain was under increased tension.

Microscopic Findings.—The nerve cells, microglia and neuroglia astrocytes were normal, but there was definite acute swelling of oligodendroglia, in a mild degree, scattered through the removed brain. The change was somewhat patchy in distribution.

Outcome.—The patient has gradually improved during the four months that have elapsed since operation and the attacks have become much less frequent, occurring now only at night; she is up and about normally. In this case, the acute swelling must have been a reversible process, although one cannot say how many of the cells returned to normal.

ANIMAL EXPERIMENTS

EXPERIMENT 1.—*Moderate degrees of acute swelling of oligodendroglia in a case of great emaciation.*

History.—This dog was operated on Jan. 17, 1924, a brain wound being made in each cerebral hemisphere. The dog appeared normal for ten months after the operation. Throughout the month of December, 1924, it ate poorly and became progressively more and more wasted, and died Jan. 8, 1925. Two hours after death the brain was fixed in situ by intra-arterial injection.

Pathologic Findings.—Aside from dense adhesions over the wound areas, nothing unusual was noted when the brain was removed. Frozen sections, stained with Rio-Hortega's strong silver carbonate solution, showed various grades of swelling of oligodendroglia (fig. 8). Many very slightly changed cells were

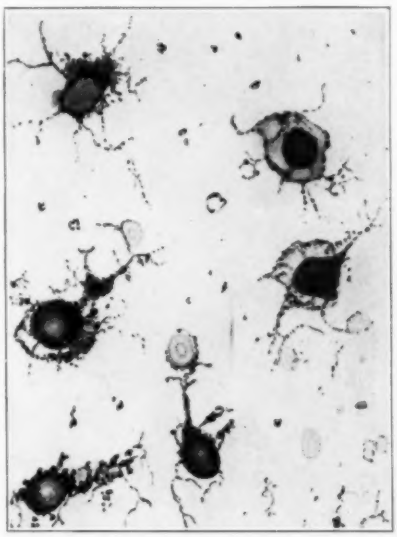

Fig. 8 (experiment 1).—Death following great emaciation in a dog: the various early stages of acute swelling of oligodendroglia present in white matter of brain; some medullary sheaths are figured in cross section. Silver carbonate stain.

present as well as many cells in the stage of moderate swelling. The perineuronal satellites were consistently swollen (fig. 9), as were also the interfascicular oligodendroglia.

Cajal's stain for neuroglia astrocytes, as well as Rio-Hortega's stain for these cells showed no change in them in either the gray or the white matter

EXPERIMENT 2.—*Acute swelling of oligodendroglia, six hours after ligation of both common carotids and one vertebral artery.*

History.—Feb. 10, 1925, at 12:45 p. m., both common carotids and one vertebral artery of a normal dog were tied off. At 6:30 p. m. the dog was examined. It responded quickly when spoken to, found a pan of water and drank from it. Its movements were slightly uncertain. At 6:45 p. m., six hours after operation, it was etherized and killed by injecting formaldehyde-ammonium-bromide upward into the carotid artery.

Pathologic Findings.—To the unaided eye the brain did not appear abnormal. Sections specifically stained for oligodendroglia showed an early swelling of these cells most marked in the white matter. The processes of the oligodendroglia cells of the gray matter could be traced for an unusual distance and the cytoplasm of these cells took the stain very densely.

The protoplasmic and fibrous neuroglia were normal for the most part. In small areas, however, in both the gray and white matter, the astrocytes showed small densely stained areas in their expansions, indicating very early clasmatodendrosis.

Note.—In another animal, ligation of both the carotid arteries produced no pathologic change.

EXPERIMENT 3.—*Extreme acute swelling of oligodendroglia bordering an area of early softening with less intense change of these cells in other parts of the brain.*

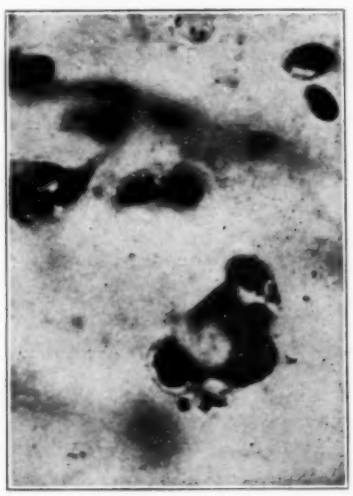

Fig. 9 (experiment 1).—Acute swelling of oligodendroglia satellites seen clustered about unstained nerve cells. Silver carbonate stain.

History.—Feb. 13, 1925, under ether anesthesia, the left common carotid artery of a normal dog was opened and black silk suture material which had been cut into very fine pieces was injected into it. The rent in the artery was then sutured. Twenty-four hours later, because the dog had been comatose since the operation, it was killed with ether. The brain was removed, immediately cut up into small blocks and placed in fixative.

Pathologic Findings.—A large area of softening in the distribution of the middle cerebral artery was found. Pieces of black silk were blocking the left middle cerebral artery and several of its smaller branches.

Microscopic examination of sections stained for oligodendroglia revealed a moderate degree of swelling of these cells, in various portions of both cerebral hemispheres. However, bordering the area of softening the oligodendroglia swelling was very great. Though the nuclei of the cells here resembled those of the cells in other sections, their cytoplasm was greatly increased in amount. Frequently there were short, thick protoplasmic projections.

Note.—In two other experimental animals similar intracarotid injections were made. No embolus resulted, however, and the neuroglia cells were found to be normal.

EXPERIMENT 4*a*.—*Early acute swelling of oligodendroglia developing after an extensive and eventually fatal abdominal operation.*

History.—Ether was given to a normal dog for three and one-half hours while an Eck fistula operation was attempted. There was considerable manipulation of the abdominal viscera and a great deal of hemorrhage occurred. The animal never regained consciousness and death followed two hours after the operation was finished. A block of the brain was removed immediately and placed in fixative.

Pathologic Findings.—Early acute swelling of oligodendroglia was found.

Note.—Experiment 9 serves as a control to 4*a*, as in that case six hours of etherization failed to produce any alteration of oligodendroglia.

EXPERIMENT 4*b*.—*Mild acute swelling of oligodendroglia present at death and increasing progressively post mortem.*

History.—A mild degree of acute swelling as the result of a long operation followed by coma and death was present in the block of brain which was removed immediately (as in experiment 4*a*). After this first piece was taken out the skull was closed again as in experiment 5 and left at room temperature. Blocks were removed and fixed at eight, twenty-four and forty-eight hours.

Pathologic Findings.—Frozen sections of the eight hour specimen showed that the early swelling of oligodendroglia noted at death had increased. Now all of the oligodendroglia cells showed swelling and in some, the increase in protoplasm was as great as that noted in the extreme examples of acute swelling. The protoplasmic projections when present were short, thick and granular.

In sections from the twenty-four hour specimen, all the oligodendroglia cells were extremely swollen. Their cell outlines were round and only a few cells showed protoplasmic projections. In some places oligodendroglia nuclei were found which had no stainable cytoplasm surrounding them.

In the sections from the forty-eight hour piece the process had progressed still further. More nuclei appeared to be free with no protoplasmic relationship. The cell outlines were less distinct and the nuclear outlines irregular.

The changes in the neuroglia astrocytes in the twenty-four and forty-eight hour sections were much less in degree than the corresponding changes noted in the oligodendroglia cells. Even in sections from the block removed forty-eight hours after death certain areas of normal appearing protoplasmic and fibrous neuroglia were to be found, while in other areas there was marked clasmatodendrosis.

EXPERIMENT 5.—*Acute swelling of oligodendroglia developing after death of normal animal.*

History.—The dog was given a large dose of chloral hydrate by stomach tube which caused death in fifteen minutes. A saw cut was made transversely through the skull so that it could be opened and closed again. A piece of brain was removed immediately at death and placed in fixative. The skull was closed and left at room temperature. A second piece was removed at the end of twenty-four hours and fixed.

Pathologic Findings.—Sections of the piece of brain removed at death and stained with silver carbonate showed normal appearing oligodendroglia in the white and gray matter. In sections from the block removed and fixed at twenty-four hours, the oligodendroglia cells among the medullary sheaths, as well as those

composing the satellite cells, showed great swelling. Many cells presented only one or occasionally two protoplasmic projections lightly outlined or filled with dark granules. Most of the cells, however, had large round vacuolated bodies with no expansions and the usual small dense nucleus.

Autolytic change in the neuroglia astrocytes twenty-four hours post mortem was typically patchy. In some areas Cajal's stain showed both the protoplasmic and fibrous neuroglia quite well preserved. In other areas much fragmentation of the glial expansions had taken place, leaving cells which presented only numerous short stumps.

EXPERIMENT 6.—*Acute swelling of oligodendroglia in a dog which died six hours after a lethal dose of guanidine hydrochloride.*

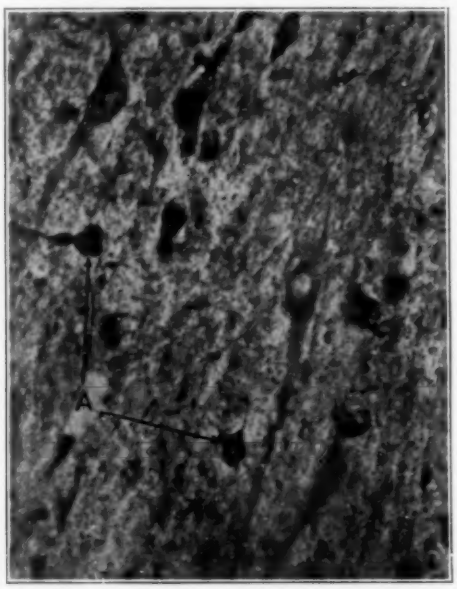

Fig. 10 (experiment 6).—Lethal intoxication with guanidine; early acute swelling of oligodendroglia, *A*.

History.—A normal dog was given 3 Gm. of guanidine hydrochloride subcutaneously. In a short time, salivation and vomiting appeared. Then tonic spasms began and occurred repeatedly. It died at the end of six hours. Thirty minutes after death the common carotid artery was injected with formaldehyde-ammonium-bromide solution. The brain was then removed, cut into small blocks and placed in fixative.

Pathologic Findings.—The oligodendroglia cells presented very early phases of acute swelling (fig. 10). Swollen oligodendroglia were scattered throughout, though many cells appeared quite normal.

In sections stained by Cajal's method, there was to be seen an early and diffuse change in the astrocytes. Small densely staining moniliform swellings were present along the course of the protoplasmic expansions. The expansions too were somewhat swollen and stained more densely than normal. The condition was the early regressive change in neuroglia astrocytes which precedes clasmatodendrosis.

EXPERIMENT 7*a*.—*Acute swelling of oligodendroglia due to guanidine intoxication (operative removal).*

History.—March 21, 10 cc. of a 10 per cent solution of guanidine hydrochloride was injected subcutaneously into a normal dog. March 22, the dog was trembling and it was evident that it had had convulsions. March 23, it was given 6 cc. of the solution above. On March 24, the dog was staggering and weak. Under ether a decompression was done and a block of brain was removed and fixed immediately.

Pathologic Findings.—There was a mild degree of acute swelling, more prominent in the interfascicular oligodendroglia than in the satellite cells.

EXPERIMENT 7*b*.—*Generalized acute swelling of oligodendroglia. Change of microglia only near wound.*

History.—The first part of this dog's history is given under experiment 7*a*. For the first three days following the removal of the block of brain, its course was apparently normal. It then developed signs of meningitis and died on the fifth day after the operation.

Pathologic Findings.—The time post mortem was not definitely known but probably was within one hour. Body heat remained and no rigor was present. Microglia appeared normal everywhere, except in the vicinity of the wound where these cells appeared in great numbers with shortened thick expansions. The transition of microglia to compound granular corpuscles within the wound itself was easily seen. The swelling of the oligodendroglia was more marked throughout the brain than it had been at operation five days before. Whether this swelling was a continuation of that due to the previous guanidine intoxication, whether it developed anew as a result of the meningitis, or whether it occurred post mortem, cannot be stated definitely.

EXPERIMENT 8.—*A second case of acute oligodendroglia change following guanidine intoxication.*

History.—This dog was given repeated injections of guanidine hydrochloride until it showed symptoms similar to those in experiment 7*a*. Then, under ether, a block of brain cortex was removed and placed in fixative.

Pathologic Findings.—The extent of the oligodendroglia changes was comparable to that in experiment 7*a*; i. e., an early swelling occurring principally in the oligodendroglia of the white matter. Sections stained with gold chloride showed normal appearing astrocytes in both the gray and the white matter.

EXPERIMENT 9.—*No alteration of oligodendroglia after six hours of ether anesthesia.*

History.—A normal dog was anesthetized for six hours. During more than half of this time the anesthesia was quite deep. At the end of the period fixative was injected into the carotid and the brain was removed and placed in the same solution.

Pathologic Findings.—None. Oligodendroglia and neuroglia astrocytes normal.

EXPERIMENT 10.—One gram of guanidine was administered daily to a dog for three days. It died on the fifth day and early acute swelling of oligodendroglia was present while astrocytes were normal.

EXPERIMENT 11.—A dog was anesthetized with morphine and chloretone for twenty-four hours. During this time there was some interference with respiration. The animal was killed and necropsy performed immediately. Moderate acute swelling of oligodendroglia was present while astrocytes were normal.

Note.—Another animal was anesthetized for twenty-four hours with morphine and chloretone but without interference with respiration, and no change in the interstitial cells resulted.

EXPERIMENT 12.—*Early hypertrophy of oligodendroglia following guanidine intoxication.*

History.—A dog was intoxicated with guanidine over a period of six days. At the end of that time a segment of brain was removed at operation.

Pathologic Findings.—Diffusely through the brain was to be found an increase in the cytoplasm of oligodendroglia. The cell body was large but without vacuoles and the knees of the expansions were quite large. It was also noticeable that the nuclei of these hypertrophied cells seemed to have changed their staining reaction so that the nuclei stained more deeply than the cytoplasm and were more pyknotic than usual.

EXPERIMENT 13.—*Oligodendroglia hypertrophy present in an animal not experimented on.*

History.—The dog was observed to be abnormally quiet but otherwise apparently in good health. A segment of brain was removed at operation.

Pathologic Findings.—The tissue showed a definite increase in oligodendroglia cytoplasm—a diffuse early hypertrophy of the cells with no vacuolization.

This animal had perhaps been subjected to some unknown toxin.

Note.—Hypertrophy of oligodendroglia as described in experiments 12 and 13 was also seen in sections from the brains of two dogs, one of which was killed eleven days and the other fifteen days, after a brain wound.

EXPERIMENT 14.—*Patchy hypertrophy of oligodendroglia after intravascular injection of water.*

History.—One hundred and twenty cubic centimeters of distilled water was injected into the saphenous vein of an adult cat. The animal was killed one hour and thirty minutes later. The brain was so greatly swollen that it caused the dura to be tense and to herniate through the first dural opening.

Pathologic Findings.—There was no vacuolization of oligodendroglia, but in patches throughout the brain the cytoplasm of these cells was definitely increased in amount, a hypertrophy resembling that already described. The nuclei of these cells tended also to be pyknotic.

EXPERIMENT 15.—*Patchy swelling of oligodendroglia with vacuolization twenty-four hours after the intravascular injection of water.*

History.—One hundred and fifty cubic centimeters of distilled water was injected into the saphenous vein of an adult cat. Twenty-four hours later the animal was killed.

Pathologic Findings.—For the most part the oligodendroglia was normal. There were, however, patches scattered through the brain in which there was definite acute swelling of these cells with vacuolization but without fragmentation.

NEGATIVE EXPERIMENTS AND CONTROLS

Shutting off all arterial supply to the head by clamping the vessels for one and three-fourths minutes just above the heart until respirations ceased and artificial respirations were necessary to revive the animals failed to produce any change in oligodendroglia in two dogs, as shown in material removed from one animal twenty-four hours later and from the other seventy-two hours after the compression.

Wormwood oil was administered to two cats, and guanidine to three cats without causing any alteration from the normal in oligodendroglia.

As shown above in experiment 9, long continued anesthesia, if uncomplicated by other factors, does not result in acute swelling. Likewise, deep drug narcosis gives a negative result if uncomplicated.

Although, as has been mentioned, in two cases some oligodendroglia hypertrophy was seen to follow nine and eleven days after the infliction of a brain wound, the change did not progress to vacuolization or fragmentation, and in four other dogs no oligodendroglia change followed experimental brain wounds. Likewise, in four rabbits these cells were found to be normal after stab wounds had been made into the brain.

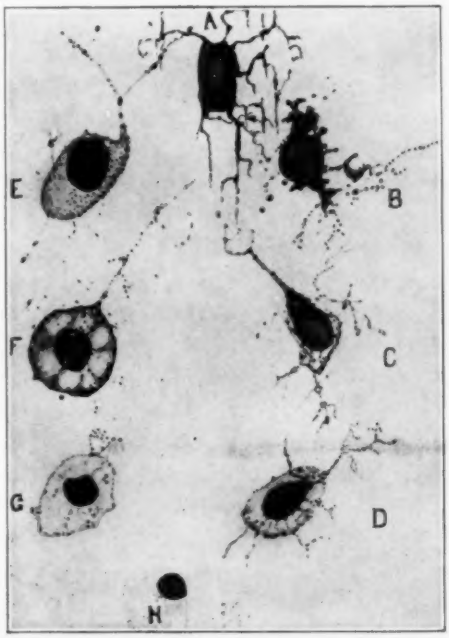

Fig. 11.—Various stages of acute swelling of oligodendroglia from normal cell, *A*, to complete disappearance of cell body leaving naked nucleus, *H*.

A negative result followed ligature of both common carotid arteries and in two cases experimental thrombosis of one common carotid was without pathologic result. Numerous normal animals were examined, in none of which were oligodendroglia changes found if necropsy was not long delayed.

Human controls were obtained from the operative material of four cases and the brain of a patient who died from trauma. That the swelling of these cells was in no sense an artefact, due to shrinkage, was proved by mounting the sections in glycerine jelly so as to avoid dehydration. The appearance of the swollen cells was the same.

COMMENT

In the process of acute swelling, oligodendroglia passes through various stages as illustrated in figure 11. The mildest change is a hypertrophy marked by increase in the amount of protoplasm of the cell

body and a pyknotic change of the nucleus. This is most striking in the cases in which the process is too mild to cause destruction. When the change is taking place rapidly there is little evidence of hypertrophy. The cell body undergoes hydropic swelling (fig. 11, *E*) and there appear unstained vacuoles outlined by granules (*C, D, F*). The expansions come to be represented by granules as the connecting protoplasm disappears. The cell body gradually disintegrates (*G*), and finally the pyknotic nucleus (*H*) remains. From the beginning, therefore, the cells seem to undergo hydropic swelling and the change resembles to some extent the acute swelling seen in the cells of other organs.

The process ends in cell destruction only if it runs its full course, but it is apparently a reversible phenomenon as shown in case 21 in which diffuse moderate swelling of oligodendroglia was demonstrated by operative brain puncture performed on an epileptic patient who afterward improved greatly. That the process is reversible is borne out by the fact that several of the experimental animals in whose brains the change was present appeared to be quite capable of making a full recovery to health, when they were killed. In experiment *7a*, in which the block of brain removed at operation showed acute swelling as the result of guanidine poisoning, the animal recovered from the operation and apparently from the guanidine, to die from a postoperative infection.

The dog (experiment 2) whose carotids and one vertebral artery had been tied ran about the room and drank water six hours after the operation, without giving other evidence of abnormality than a slight uncertainty of movement. Yet there was a mild, diffuse, acute swelling of oligodendroglia in the brain at that time.

Acute swelling may be caused purely by autolytic conditions as in the case of the brain which was normal at death but which developed diffuse acute swelling after twenty-four hours without fixation. Or it may be in part autolytic, as in the brain which presented slight acute swelling at death and increased swelling after eight hours without fixation. That extreme degrees of acute swelling may be present during life is shown in the case of sarcoma of the leptomeninges in which necropsy was performed three-quarters of an hour post mortem, and in that of tuberculous meningitis in which necropsy was performed after two hours. These were among the most extreme examples of acute swelling. Complete proof that the change occurs in "fullblown" form intra vitam is also to be had from the animals, several of which were killed by carotid injection of the fixative, and also from animals in which pieces of brain were removed at operation and fixed immediately.

It is quite possible that the change may frequently have been agonal, as in the cases of carcinoma of the stomach and of cardiac decompensation with death in stupor, and the animal which succumbed in six hours

to a large dose of guanidine (experiment 6). Moreover, the dog (experiment 4) which died in five and one-half hours as a result of etherization and operative hemorrhage showed the change, whereas, in another experiment (9) six hours of etherization which did not result in death failed to produce any change in the brain.

The production of extreme swelling of the brain by intravascular injection of distilled water resulted in only the slightest detectible alteration of oligodendroglia. Therefore, the change is evidently not due to simple edema.

Human control material was obtained from operations and from necropsy material following traumatic death. Some degree of swelling will usually be found in routine necropsy material and this may be associated with the fact that somnolence or stupor is the almost invariable precursor of death in hospital cases. But unless the mental change is marked and of some duration, the degree of diffuse oligodendroglia swelling has never been extreme in our experience with thirty cases. It seems fair to predict that in the brains from cases of toxic delirium due to various causes, acute swelling of oligodendroglia will be found consistently.

Finally, this change in oligodendroglia appears in the central nervous system as a response to pathologic conditions which influence the brain in a toxic manner. This is seen both clinically and experimentally. It is present in some epileptic conditions and occurs as an agonal change in cases in which death is preceded by coma or stupor of several hours' duration. It will invariably appear if fixation is delayed too long after death.

If the regressive change in oligodendroglia is sufficiently severe it is always accompanied by clasmatodendrosis of astrocytes (ameboid glia) but the conditions which thus influence neuroglia do not affect microglia. This may be taken, perhaps, as suggestive biologic evidence in favor of the contention that the latter cells have an origin different from that of neuroglia.

Although similar in certain ways to clasmatodendrosis, acute swelling of oligodendroglia appears before any change in the astrocytes and often is the only evidence of a pathologic change discoverable in the brain.

THE FOREBRAIN AND MIDBRAIN OF THE ALLIGATOR WITH EXPERIMENTAL TRANSECTIONS OF THE BRAIN STEM

A STUDY OF ELECTRICALLY EXCITABLE REGIONS *

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There has been some previous evidence that in reptilia we have, in addition to a mesial cortical area, which is probably olfactory, the early development of other cortical correlation centers, the beginning of a neopallium. The elder Herrick has, without going into any speculations of functional assignments, suggested the appearance of a visual cortex. Edinger, Meyer,[1] Brill [2] and others distinguished a mesial, a lateral and an intermediate region of cortex. Crosby,[3] demonstrated this division in histologic preparations in the alligator at about the same time that Johnston [4] showed that stimulation of an area of the cortex in turtles and lizards caused very definite movements of the extremities without, however, identifying the region with one of the histologically determined fields. A recent paper by one of us [5] reported the results of stimulation of the forebrain of the alligator.

In our previous experiments the brain was exposed in seven alligators and the cortex stimulated with a bipolar electrode, using a mild induced current. Motor responses were obtained from a relatively wide area on the dorsomesial surface of the hemisphere (fig. 1), the boundaries not corresponding exactly to those described by Johnston [4] nor coinciding with the cortical districts of Crosby.[3] Our area includes the anterior part of what the latter calls "general cortex," but extends mesially into the hippocampus and laterally into the region of the pyriform lobe.

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* From the Neurological Laboratory of the Henry Phipps Psychiatric Clinic, the Johns Hopkins University.

* Read before the Fifty-First Annual Meeting of the American Neurological Association, at Washington, D. C., May, 1925.

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2. Brill, N. E.: The True Homology of the Mesial Portion of the Hemispheric Vesicle in the Sauropsida, M. Rec., March 29, 1890.

3. Crosby, E. C.: The Forebrain of Alligator Mississippinesis, J. Comp. Neurol. **27**:325-402, 1916.

4. Johnston, J. B.: Evidence of a Motor Pallium in the Forebrain of Reptiles, J. Comp. Neurol. **26**:475, 1916.

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Stimulation of this region caused a general flexion of the tail toward the side stimulated and flexion of the legs, particularly on the contralateral side. The head was turned toward the opposite side (fig. 2). Movements were more pronounced when the cortex was stimulated near the midline. It was impossible to elicit movement of any single extremity by itself—all the movements elicited were of the mass variety. In general, it could be said, however, that the mesodorsal part seemed to be responsible for the head and tail movements, while the outer portion of the area favored movements of the legs.

FURTHER EXPERIMENTS IN FOREBRAIN AND MIDBRAIN STIMULATION

Since the preliminary report was published, twenty-six additional experiments have been made, first to determine the presence of other excitable areas in the alligator brain, and secondly, to study the effect of removal of the excitable regions on the movements of the animal.

Fig. 1.—Small dots indicate the extent of the surface which gave positive electrical results; the inner part of the area was most responsive.

Practically all this series of operations was done with sterile precautions. The alligator is relatively immune to infection; many of the animals lived and were studied over periods of from one to twenty-one days. The outer table of the skull was cut in the midline with a chisel under cocaine anesthesia and two flaps were turned laterally. This opened huge air sinuses covering the cranial vault. The inner table of bone covering the brain was then carefully removed with a rongeur until an adequate exposure was obtained; it was found that with care a large vein lying between the forebrain and midbrain could be separated from the dura and unnecessary hemorrhage avoided. After the operation the escape of cerebrospinal fluid was controlled by the application of fresh muscle. The outer table of the skull was then replaced and held in position by adhesive strips. This was found to give a very satisfactory closure. No anesthesia was employed during the period of electrical stimulation. With experience it was easy to distinguish typical motor responses, the result of electrical stimulation, from nocuous responses

due to spread of the current to the dura and other peripheral structures. Any questionable reactions were immediately ruled out.

The first procedure in this series consisted in the separation of the area shown in figure 1 from the surrounding cortex except at its mesial extremity. This tongue-like flap was reflected on the opposite hemisphere and its under surface stimulated, after placing under the flap a piece of mica to prevent the spread of current to the underlying hemisphere. Stimulation of the flap gave the same reactions as those recorded in the normal brain, while stimulation of the exposed corpus striatum mass gave negative results. Moreover, if the cortex was cut away so that it was attached to the underlying structures only laterally, electrical stimulation gave no motor reaction. This experiment proved beyond doubt that the reactions described in our previous work were not due to stimulation of the striatal structures lying immediately under the ventricles, beneath the thin cortical sheet or convexity. The corpus

Fig. 2.—The position of the alligator after stimulation of the right forebrain area as shown in figure 1.

striatum mass was then removed piecemeal, so that stimulation of this body at various levels was possible. At no point, however, were reactions obtained. The removal of the corpus striatum brought into full view the mesial wall of the hemisphere. Stimulation of this wall gave results similar to those recorded after cortical stimulation, but usually with less current in accordance with the fact that the fibers from the convexity run down the mesial wall, fornix fashion. After complete removal of the corpus striatum, application of the electrode to the remaining stump seemed, at first, to give a nocuous response, but later experiments led us to believe that this was due to spread to the midbrain which lies very close.

In searching for additional excitable areas it was found that very typical motor responses could be obtained when the midbrain was stimulated. The posterior part of the dorsal surface of this structure seemed even more easily excited than the region in the forebrain already described. A current sufficiently strong to produce reactions in the

forebrain would in the midbrain produce violent movements. When the current was reduced to approximately one-half, the movements were slow and rhythmic and could be controlled by the application and removal of the electrode. Here again, as after forebrain stimulation, movements of single extremities could not be constantly obtained. In general, the reflex pattern was as follows: moderate pulling of the tail to the same side, flexion of the contralateral hind-leg and slight flexion of the ipsilateral fore-leg. It was noted that midbrain stimulation caused lateral deviations of only the tip of the tail (fig. 3).

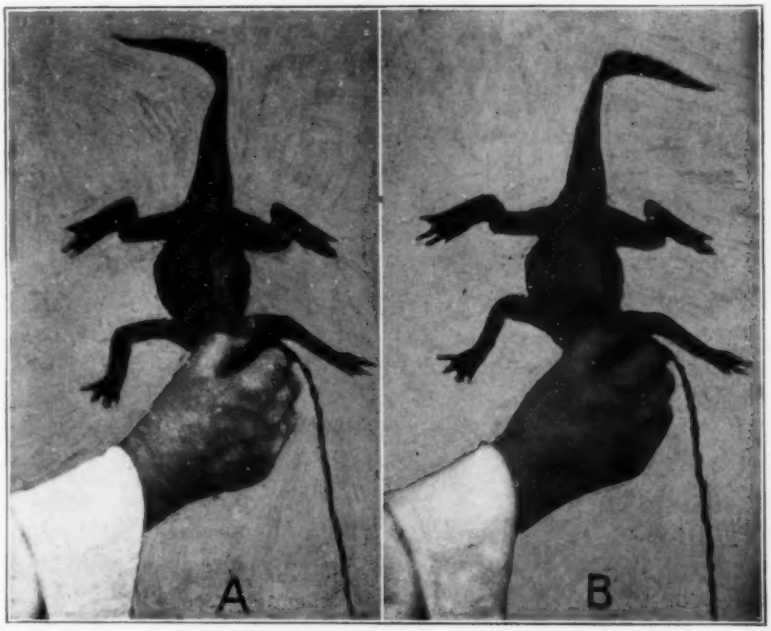

Fig. 3.—*A*, stimulation of the right midbrain with pulling of the tip of the tail toward the same side; *B*, stimulation of the left midbrain with pulling the tip of the tail toward the left. This is in contrast to the complete pulling around of the tail following stimulation of the forebrain area (fig. 2).

In the cortex of the forebrain of the alligator, therefore, there was a well defined area, electrical stimulation of which gave not movements of single extremities, but mass movements of a rather definite reflex pattern. In the tectum opticum of each side there was located a second excitable area—this area was perhaps, of greater motor value in that the reactions were obtained with less current than was necessary in the forebrain area.

The possibility of the stronger current used in the forebrain area spreading to the midbrain area has been considered; but the fact that

these reactions were not obtained, even when a stronger current was applied to more caudal parts of the cortex and in close proximity to the midbrain area, leads us to believe that the areas in the cortex are independent of each other.

An effort will be made to explain these reactions on a structural basis. De Lange [6] studied the nuclei and tracts in the diencephalon and mesencephalon of the alligator and other reptiles. He corroborated the findings of Adolf Meyer,[7] Herrick, and others, that the axons from the larger cortical cells are typical fornix or mesial wall radiations ending around cells in the habenular and mammillary nuclei. They must, therefore, exert their influence on the segmental mechanisms by means of additional neurons. The arrangement has nothing in common with the direct corticosegmental or pyramidal path of the mammals.

Large numbers of efferent cells were found by De Lange in the well developed tectum opticum of the midbrain. The axons from these cells form large tectobulbar and tectospinal tracts. Less than half of these fibers decussate in the tegmentum. Thus there is, in the roof of the midbrain, a large center for motor coordination directly under the influence of optic stimuli and efferent tracts of the first order to more caudal segments. As an expression of this mechanism, stimulation of the tectum opticum gave definite movements of the extremities. The excitable parts here seem coordinated to join definite reflex patterns suitable for alternate progression.

In addition to stimulation experiments carried out under local anesthesia, experiments under general anesthesia were undertaken. Chloroform was used. Anesthesia was not difficult to produce but care was necessary to avoid carrying it too far. Stimulation of the forebrain in anesthetized animals gave the usual response in the extremities, but a stronger current was required and the movements were very jerky and not easily controlled by the application and removal of the electrode. For example, alligator 18 was stimulated, Sept. 24, 1924, under general anesthesia. Reactions were obtained at a point on the induction apparatus ranging from 6 to 8.5 cm. The following day the same animal was stimulated without general anesthesia and typical reactions were obtained from 8.5 to 10 cm. The same alligator was again stimulated without general anesthesia, September 29, and typical reactions were obtained from 9.5 to 10.5 cm.

From these experiments it is evident that the reactions obtained from electrical stimulation of the motor cortex of reptiles are of a

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6. De Lange, S. J.: Das Zwischenhirn und das Mittelhirn der Reptilien, Folia neurobiol. **7**:67, 1913.

7. Meyer, Adolf: Zur Homologie der Fornix Commissur und des Septum Lucidum bei den Reptilien und Saugern, Anat. Anz. **10**:474-482, 1895.

very primitive type as contrasted to those of mammals. For example, in the ungulate brain, cortical areas were outlined by Bagley [8] which, on stimulation, gave responses in the extremities and occasionally in the trunk. Individual areas for the four extremities could not be differentiated, but movements of the opposite hind-leg together with the fore-leg of the stimulated side frequently occurred. In the most caudal portion of the area for the extremities, reactions in the hind-leg predominated, while fore-leg reactions were most frequent in the area immediately cephalad. A separate area, which, when stimulated, produced movements of the head and eyes to the opposite side, was outlined. In addition, two distinct areas, one for the movement of the face musculature of the same side and the other for the face musculature of the opposite side, were demonstrated.

An increasing refinement of these motor cortical reactions is evident as we study higher mammals until they reach their greatest development in the anthropoid apes and man. In the alligator we see this motor area in its early development, before the corticospinal tract has yet appeared, giving rise on stimulation to rather gross reactions. There is also an important excitable area in the roof of the midbrain correlated with optic and other afferent fibers.

EXPERIMENTAL TRANSECTIONS OF THE BRAIN STEM

Experimental transections of the brain of mammals have given us information concerning the mechanism controlling posture and progression. The phenomenon of decerebrate rigidity, first demonstrated by Sherrington [9] in 1896, has been the subject of much investigation since, not only because of its similarity to certain spastic paralyses seen in the clinic, but because it gives an insight into some phases of motor control. If the brain of the dog or cat is transected through the midbrain, the preparation assumes an extensor attitude, the legs are stiffly extended, the head retracted, and the tail dorsiflexed or extended. This is the reflex posture of standing and was considered by Sherrington as essentially a manifestation of an antigravity reflex. The center for this extensor mechanism lies principally in the midbrain; many believe that the cells of the red nucleus are chiefly concerned. Bazett and Penfield,[10]

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8. Bagley, Charles, Jr.: Cortical Motor Mechanism of the Sheep Brain, Arch. Neurol. & Psychiat. **7**:417 (April) 1922.

9. Sherrington, C. S.: On Reciprocal Innervation of Antagonistic Muscles, Proc. Roy. Soc. **60**:414, 1896.

10. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as in the Acute Condition, Brain **45**:185 (Oct.) 1922.

and Magnus and de Kleijn consider, however, that the red nuclei are not necessary for the maintenance of decerebrate rigidity.

Obviously, it would be valuable not only to know the complete path for this reflex, but also to understand more fully its relation to the remainder of the motor apparatus. As decerebrate reactions have until now been largely studied in the higher mammals, it seemed interesting to reveal them possibly in a more primitive form in lower mammals and even in premammalia. Information concerning these motor responses in the lower mammals is becoming available. Reports have been published dealing with the motor mechanism of the opossum, a marsupial, by Rogers, and by Weed and Langworthy.[11] The motor cortex in this animal is primitive in comparison with that of higher mammals. For while stimulation of the cortex with a stigmatic electrode with mild induced current elicited ipsilateral movement of the facial musculature and flexion of the ipsilateral fore-leg from well-defined areas, the observations of earlier observers were confirmed that no center for the hind-legs existed.

After decerebration, in the opossum, definite rigidity appeared in the fore-legs and strong rigidity in the tail. Rigidity in the hind-legs, however, developed at a later period and was always rather weak and transient in character. Moreover, the opossum did not maintain the immobility seen in the decerebrate cat, for periods of activity occurred when the animal showed progressive movements of the legs and the rigidity entirely disappeared. No extensor rigidity was observed in young opossums for at least the first two months after birth. Kittens at birth will not display the phenomenon of decerebrate stiffness, but it soon develops (Weed[12]). The relation of the time of development of this postural reaction to the maturity of the nervous system of young animals has been considered by Langworthy.

Since Flourens' classic work on the pigeon, many observations have been made on birds after removal of portions of the central nervous system. Rogers[13] recently studied the complex instinctive behavior of pigeons after removal of the hemispheres, the corpora striata and even partial removal of the thalami. His experiments, however, deal very little with the particular aspect of the problem in which we are at present interested.

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11. Weed, L. H., and Langworthy, O. R.: Developmental Study of Excitable Areas in the Cerebral Cortex of the Opossum, Am. J. Physiol. **72**:8 (March) 1925; Decerebrate Rigidity in the Opossum, ibid. **72**:25 (March) 1925.

12. Weed, L. H.: The Reactions of Kittens After Decerebration, Am. J. Physiol. **43**:131 (April) 1917.

13. Rogers, F. T.: Regulation of the Body Temperature in the Pigeon and Its Relation to Certain Cerebral Lesions, Am. J. Physiol. **49**:271 (July) 1919.

Steiner,[14] working on lizards (*Lacerta viridis*), transected the brain at various levels. After removal of the brain at the level of the thalamus the lizard remained perfectly inactive; if urged, the animal moved apparently normally, but after two or three steps made a jumping movement with head bowed backward and tail raised, as the normal animal does when pursued or when it jumps from a height. When not stimulated it again becomes quiet. He found that vision was impaired after lesions of the thalamus, for if the thalamus was removed on one side the lizard avoided obstacles on that side, but was totally unaffected by obstacles mirrored in the contralateral eye. On removal of the whole midbrain, the animals were blind, whereas elimination of the cephalic half of the midbrain did not cause absolute blindness. He, therefore, assumed that, in contradistinction to the frog and fish in which vision is apparently entirely subserved by midbrain centers, the lizard has developed an additional visual center in the thalamus. We have made no observations on vision in our alligator experiments.

After removal of the roof of the mesencephalon, the motility of the animal was in no wise disturbed. Removal of half of the midbrain started the animals uniformly and with great ease on retrograde progression. Transection of one half of the mesencephalon caused circular movements toward the opposite side—identical with those occurring after a similar lesion in the frog and fish. Steiner, therefore, postulated a general motor center in the midbrain, a mechanism so arranged that its elements can produce movements in all desirable combinations, the kind of combination being largely determined by peripheral stimuli Steiner's experiments on the lizard furnish facts concerning a general motor center extending below the midbrain into the medulla.

The first operations in this group had to do with the removal of the cerebral hemispheres and basal ganglia. The pia was carefully opened and these structures scooped out with a curet to avoid troublesome bleeding. In the first series care was taken not to injure the thalamus. This operation had little effect on the motor activity of the animal. The alligator was quite able to stand on its legs, and voluntary progressive activity of the normal alternating type was observed. Similarly removal of all structures down to the midbrain, including the thalamus, seemed to have no effect on the posture and normal progressive activity of the alligator. As these are cold-blooded animals, removal of the thalamus did not cause the serious effects produced in warm-blooded animals, in whom the heat regulating mechanisms are injured, and no particular care was taken to keep the animal warm. It will be noted that this same

14. Steiner, Isador: Die Functionen des Centralnervensystems und ihre Phylogenese (Part 1). Untersuchungen über die Physiologie des Froschhirns. Vierte Abtheilung (Schluss) Braunschweig, 1885-1900, p. 143.

type of injury in mammals elicits the phenomenon of extensor rigidity. But in the alligator no rigidity was noted at any time. The animal balanced his weight normally on his four legs and exhibited at times spontaneous progressive movements quite similar to those seen in normal controls.

One curious reaction was noted in these preparations: the animals tended to turn persistently toward one side. Most of them kept the head and body curved to the right and walked toward the right; a few also turned toward the left. Now in experiments of cerebral stimulation, it was noted that reactions from one hemisphere, usually the left, could be obtained with less current, and fatigue developed later than in the

Fig. 4.—Saggital section through the alligator brain showing at *a* the line of division in the midbrain experiments.

Fig. 5.—Animal after division at the level of the midbrain showing extreme extension of the forelegs which develops when an attempt is made to walk.

other. Whether the irritation of the cut fibers of a predominant hemisphere caused the animal to turn to the opposite side or whether this reaction was simply due to some irritation such as hemorrhage, the result of the operative procedure, it is impossible to say.

The group of alligators with which we are particularly interested, however, is one in which the transection was made through the lower end of the midbrain severing the medulla from all structures cephalad to it. The completeness of this section was always confirmed at necropsy (fig. 4). Alligator 26 when placed on the floor, immediately after operation, took three or four steps in a normal manner. During these progressive movements a powerful extensor mechanism came into play.

The legs became at each step more and more extended until finally the animal came to rest like a statue, high on all four legs with the head rigidly retracted. Development of this extension seemed in itself to inhibit further progression and the animal would stand quiet in this position for three or four minutes. A photograph of such an immobile animal is given in figure 5.

No normal animal was ever observed to stand in this manner; normally the fore-legs are slightly and the hind-legs considerably flexed.

Fig. 6.—Extreme extension of the legs makes posture unstable when walking.

Fig. 7.—Balance lost; animal has fallen on the right side.

Passive movement of the head up or down or to the side produced changes in posture similar to those described by Sherrington in the decerebrate cat. These postural adjustments have recently been studied in great detail by Magnus and de Kleijn, Walshe and others.

If the preparation was now stimulated strongly until the animal attempted to walk, one of the fore-legs would give way and he would fall forward and to the side (figs. 6 and 7). Many of the animals fell invariably to the right; one fell to the left. In this extensor position no coordinated walking movements were possible. The animals remained relatively immobile, and attempts at progression could be initiated only by strong sensory stimuli.

This extensor phenomenon only developed when the animal attempted to walk. When it lay undisturbed the legs were flexed and it maintained its posture in a normal manner. Nor was there much resistance to passive motion of the extended limb. The tail seemed to be unaffected. One of the animals operated on lived for ten days. There was no change in the reflex activity during this time.

COMMENT

In reptiles, according to De Lange,[6] there is a well-developed red nucleus, the cells for the most part belonging to the large cell type. In only one species did De Lange find a definite group of small cells in the cephalic portion of the nucleus. However, a few small cells were present in all the species studied and there was a scattering of these cells in the alligator. In higher mammals the red nucleus may be divided into a cephalic small cell portion and a caudal large cell portion. Von Monakow believed that the small cells develop coincidently with the development of the cerebral hemispheres. To this small cell group has been attributed the maintenance of decerebrate rigidity.

Is it possible to correlate the extensor phenomenon seen after removal of all structures cephalad to the rhombencephalon in the alligator with any extensor reaction in higher mammals? Many observers believe that the midbrain and particularly the red nucleus must be intact for the prolonged maintenance of decerebrate rigidity in mammals. Bazett and Penfield,[10] however, observed rigidly in cats in which the whole midbrain including the red nucleus had been put out of function. This rigidity was not constantly present but appeared on the application of sensory stimuli.

Cobb,[15] Bailey and Holtz concluded that the red nucleus must be present for the maintenance of strong, constantly maintained extensor rigidity. Some rigidity, however, remained after the midbrain was removed; this was not constantly present, but could be induced by manipulation of the extremities. Section of the brain at about the level of the eighth nucleus abolished all rigidity. They hypothesized that the center for this second type of rigidity must be Deiters' nucleus.

The extensor phenomenon in the alligator is apparent only after complete removal of the midbrain. It is not constantly present, but develops after any attempt at progression. It affects the legs and neck. There is little resistance to passive movements of the extremities. When extension is well developed coordinated progression is impossible and the alligator remains immobile in the extensor position. If walking is now attempted, balance is lost and the animal falls on its side.

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15. Cobb, S.; Bailey, A. A., and Holtz, P. R.: Genesis and Inhibition of Extensor Rigidity, Am. J. Physiol. **44**:239 (Sept.) 1917.

Certainly the reaction of the alligator does not resemble that of the decerebrate cat in which the midbrain is intact. It bears more resemblance to the cat described by Cobb in which all structures cephalad to the hind brain have been extirpated. In fact the reactions of these two preparations seem quite analogous.

The alligator experiments bring to our attention one other problem, namely, the question of release. In order to demonstrate decerebrate rigidity in mammals, it is necessary to cut off motor impulses from the prosencephalon. When the cerebral hemispheres alone are removed coordinated progressive movements occur. When the thalamus is also ablated well maintained rigidity develops. Weed [12] found, by physiologic experiment, a tract arising in the cerebral cortex having an inhibitory effect on the rigidity. The fibers run in the mesial portion of the cerebral crus, cross, and end around cells whose fibers enter the cerebellum through the middle peduncle. In the cerebellum they probably end in an inhibitory center first discovered by Sherrington [9] in the superior vermis. This center through connections as yet not understood inhibits decerebrate rigidity. Not only must this inhibitory tract be severed but also the influence of the thalamic area must be removed before the extensor rigidity may be demonstrated.

In the alligator, in which the principal final motor coordination is possible from lower levels, the extensor mechanism must likewise be released by severing the influence of higher centers. Thus, cutting off the rather insignificant motor control of the prosencephalon does not grossly upset the motor mechanism. We must remove the relatively important midbrain centers before any increased extensor function can be demonstrated. The highest centers of motor coordination preserve an equal balance between flexion and extension. When they are removed we have a disturbance of balance in favor of the extensor elements.

SUMMARY

Cortical stimulation of the forebrain of the alligator gave the same motor responses as those previously reported. Stimulation of the mesial wall of the cerebral hemispheres produced movements similar to those obtained from the cortex, even with slightly less current. Stimulation of the corpus striatum area gave negative results over its upper portion and at various levels after fractional removal. In each midbrain colliculus or tectum opticum there is an area more responsive to electrical stimulation than that outlined in the forebrain.

Under anesthesia a greater amount of current was required to produce reactions and the movements were not so well controlled; our results were, therefore, more dependable when the animal was not under general anesthesia.

When the alligator's brain is transected at the caudal end of the midbrain, releasing the rhombencephalon from all cephalad impulses, a curious extensor mechanism is revealed on any attempt at progression. With the first few steps the legs become more and more extended to the point that progression activity is inhibited and the alligator remains immobile like a statue, high on all four legs with the neck rigidly retracted. Passive movement of the head produces postural changes similar to those reported by Sherrington in decerebrate cats. If now progression is attempted the animal invariably loses its balance and falls to the side. There is little resistance to passive movement of the extended legs.

MENINGO-ENCEPHALITIS DUE TO TORULA*

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Invasion of the cerebrospinal axis by fungi related to the yeasts (blastomycosis, oidiomycosis, coccidioidal granuloma) has been often reported. Cases showing skin lesions, with systemic infection, have been frequent. The rarity of cases in which, clinically, the nervous system alone was involved prompts us to report this study of a single case.

When one attempts to classify fungi that are pathogenic to man, one finds great confusion. The term blastomycosis has been loosely used to cover all types and no serious attempt to clarify the situation was made until Stoddard and Cutler [1] produced their splendid monograph in 1916. They emphasized the tissue reactions and the cultural characteristics of the various types, and arrived at definite conclusions concerning the differential features of infection by saccharomycetes, torula and oidiomycosis. There are many points of resemblance in the pathologic lesions, but Stoddard and Cutler pointed out that classification can be made by clinical and histopathologic studies.

Recently Shapiro and Neal [2] have reported a case of torula meningitis in which extensive bacteriologic studies and animal inoculations were made. In their case the etiologic relationship of torula was established beyond doubt. They report fourteen cases of torula infection from the literature, their case being the fifteenth.

Although cultural studies were not made in our case, owing to the impossibility of procuring more than one specimen of spinal fluid, and although the postmortem examination was limited to the brain, we are confident that the organism was a torula, because of our clinical and histopathologic findings. This is the sixteenth recorded case as far as we can learn. Fourteen of the cases previously described involved the central nervous system.

For the sake of convenience and brevity, an attempt is made here to present in tabulated form the chief differential features of yeast fungi.

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* Read by title at the fifty-first annual meeting of the American Neurological Association, Washington, D. C., May, 1925.

1. Stoddard and Cutler: Torula Infection in Man, Monogr. Rockefeller Inst. M. Research **6**:1-98 (Jan. 31) 1916. In this monograph will be found a bibliography essentially complete to the year of its publication.

2. Shapiro, L. L., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. **13**:174-197 (Feb.) 1925.

Differential Features of Yeast, Torula, Oidiomycosis and Coccidioidal Granuloma
(Modified from Stoddard and Cutler, and Shapiro and Neal)

	Genus	Reproduction	Sporulation	Mycelium	Sugars	Pathogenicity	Lesions	Pathologic Characteristics	Size of Organism, Microns
Fungi Imperfecti — Blastomycetes	Saccaromycetes.. .... (true yeasts)	Buds	Ascospores present	Absent	Fermented	Feeble	Skin	Necrosis; epithelial overgrowth; giant cells; abscess formation; polymorphonucleosis	....
	Torula.....	Buds	Absent	Absent	Usually not fermented	Moderate	Nervous system; other organs to less extent; skin never	Chronic inflammation; caseation occasional; no polymorphonucleosis; gelatinous matrix	1–13
	Monilia.	Buds	Absent	±	Fermented	Moderate	Mucous membranes; mouth and gastrointestinal tract; slight skin pigmentation	Chronic ulceration	5–10
	Oidiomycosis.....	Buds	Absent	Present	Not fermented	Slight	Skin always; often bones, internal organs and brain	Necrosis; epithelial overgrowth; miliary abscesses; tubercle-like nodules; polymorphonucleosis; no gelatinous matrix	3–30
	Coccidioidal granuloma...	Never buds	Endospores present	Present with aerial hyphae	Not fermented	Marked	All organs; often skin	Nodules and cysts; giant cells; caseation; abscess formation; polymorphonucleosis; no gelatinous matrix	5–85

Torula is a pseudo-yeast, occurring abundantly in nature, on trees, on fruits, on bees' and wasps' nests and on the insects themselves. It has been found in canned butter by Rogers [3] and in milk by Klein.[4] It varies in diameter from 1 to 13 microns, is spherical or oval in shape, reproduces only by budding, and never produces mycelium or endospores. It usually does not ferment sugars. It is more pathogenic for man than the true yeasts. It never produces skin lesions and shows a striking predilection for the central nervous system and lungs. This is an important point for clinical differentiation.

The symptoms presented usually point to the cerebrum. The mode of infection is uncertain, but the most probable point of entry is the respiratory system, and the subsequent path of distribution is through the lymph and blood stream. There is evidence that the spread of the infection in the brain takes place along the perivascular spaces.

The clinical history and findings are those of a subacute inflammatory disease of the brain, with more or less meningitic reaction, involving to a variable extent all structures of the white and gray matter. There is no fever in the early stages and no leukocytosis. The organisms have been recovered from the spinal fluid in six cases but they do not always appear early in the disease. The progress is steady and the disease, in all cases thus far reported, has terminated fatally. The inflammatory edema associated with the pathologic lesions apparently produces tissue destruction by pressure.

When confronted with the organic neurologic signs and symptoms that accompany torula infection, the physician, without the aid of spinal fluid findings, has a perplexing problem. The possibility of brain neoplasm, multiple sclerosis, epidemic encephalitis, basilar meningitis, etc., at once arises. It is only through repeated cytologic and cultural studies of fluid specimens that the diagnosis can be established during life.

While this type of infection of the central nervous system is rare,[5] the well established cases being only sixteen in number, we should be on the alert for them. Furthermore, it seems to us, once detected, the problem of effective therapy opens a fruitful field for investigation. Intravenous administration of iodide has proved of specific value in oidiomycosis, but effective therapy for torula infection is not known.

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3. Rogers, L. A.: A Fat-Splitting Torula Yeast Isolated from Canned Butter, Abst. Sci. **17**:370, 1903.

4. Klein, E.: Pathogenic Microbes in Milk, J. Hygiene **1**:78, 1901.

5. References to other articles relating to this subject will be found in the author's reprints.

The case described here presented many perplexing problems, but could have been definitely diagnosed during life if the patient's condition had warranted more extensive study.

REPORT OF A CASE

The patient, a woman, aged 50, single, was admitted to the Neurological Institute, Jan. 22, 1924, complaining of drooping of the eyelids, disturbance of vision, headache with pain localized over both eyes, and vomiting.

Clinical History.—In September, 1923, the patient noticed that she could not see as well as formerly, although her vision had always been blurred as the result of an infection of the corneas with subsequent scarring, which had forced her to hold objects close to her eyes in order to see them; this difficulty had been increasing. She saw double at times. Two days after the onset her right eyelid drooped, and since then she had been unable to raise it except very slightly. Because of the drooping of the right eyelid she had not been able to read with that eye. Within a few days she complained of excruciating pain over the right eye, the top of the head and at the back of the neck. The pain was constant and was intensified by lying down; it was somewhat relieved by sitting up. The patient had to be given a sedative to relieve the pain. The pain was accompanied by nausea, which the patient believed was caused by medicine. On two or three occasions she vomited after taking codeine; the vomiting was not projectile in character. The headache continued for four weeks.

From October to December the patient felt quite well, except for the drooping of the right eyelid. In the later part of December, 1923, she again complained of headache, with pain over the left eye, the top of the head and the back of the neck. The headache was constant and was made worse by lying down. The patient said she felt as though a heavy weight had been placed on her head and seemed to be crushing her down. This acute attack subsided in a few days. About Jan. 1, 1924, the patient noticed difficulty in raising the left eyelid. Dizziness was quite marked for two weeks previous to admission. Throughout her illness, the patient had been able to take walks, but since the onset of dizziness she had remained quiet for fear she would fall.

Past History.—The family history was unimportant. There was no history of trauma, unconsciousness, convulsions or paralysis other than that noted above, and there were no diseases relating to the present symptoms. There had never been any complaints referable to the kidneys or lungs. The patient had had frequent attacks of pharyngitis, but none immediately preceding this illness. The patient took tea moderately, and did not indulge in coffee, tobacco or alcohol. Her appetite and bowls were normal. Menstrual periods had been normal until six years before admission when they ceased. There was no sphincter disorder.

Physical Examination.—When first examined the patient was able to walk, there was nothing abnormal in her attitude and there were no deformities. There was noticeable only a tendency to walk with her head to the right. The gait was normal forward and backward, on the heels and on the toes. In walking and during the examination, it was noted that the frontalis muscle was used to elevate the eyelids. Standing with the feet together or on one foot was normally performed with the eyes open or closed. There was no past-pointing. The finger-to-nose, finger-to-finger and each finger-to-thumb tests were well performed with both hands. The heel-to-knee and toe-to-object above the recumbent patient tests were also normally executed. There was no adiadokokinesis. There was very slight awkwardness in using the left hand. There was no dysmetria.

The patient was right handed. The hand writing was not tested. Spontaneous speech was normal; test phrases were normally enunciated, and there was no fatigability of the speech musculature. Muscle strength, movement and tone were normal in the extremities, and there was no atrophy. No abnormal involuntary movements were observed.

Reflexes.—The deep reflexes of the upper and lower extremities were present, equal on the two sides and normally active. The superficial reflexes, including the upper and lower lateral abdominal and the plantar responses, were present and equal. The Babinski and corroborative signs were present.

Sensory findings: Touch acuity and localization, pain, temperature, vibratory, muscle and tendon sensibilities were all normal.

Cranial nerves: I. There were no disturbances in the sense of smell.

II. The patient had no difficulty in counting fingers at six feet, but in reading ordinary print had to hold the book close to her eyes. The fields were normal to rough tests. The fundi showed considerable pallor in the temporal portions of the disks but the edges were distinct and the vessels apparently normal. The fundi had been examined a week previously and no differences were noted between the two examinations.

III, IV and VI. The pupillary diameters were 6 mm. on the left and 5 mm. on the right; the pupils did not react to light, convergence was impossible, and there was no consensual reaction. No exotropia was observed, but slight exotropia on the left had been present a week previous to this examination. There was moderate exophthalmos on both sides. A week previously the only motion possible in any direction had been to the left with the left eye; at this examination all motion had disappeared. There was no nystagmus. Bilateral ptosis was present; at times the patient was able to open the eyes very slightly, the right more so than the left.

VIII. To ordinary voice sounds there was no defect in hearing; bone conduction was greater than air conduction on both sides.

V, VII, IX, X, XI and XII. The remaining cranial nerves showed no evidence of abnormality.

Mental status: The mental condition was normal.

Cranial morphology: No abnormalities could be detected by palpation or by inspection.

Systemic examination: The tegumentary system was normal. There were no glandular disturbances. The pulse rate was normal; the blood pressure was 150 systolic and 90 diastolic. The heart, lungs, gastro-intestinal tract, genito-urinary system, and skeletal system showed no abnormalities.

Laboratory Examinations.—Hemoglobin, 75 per cent; red cells 5,000,000, white cells 7,000 per cubic millimeter; neutrophils 74 per cent, small lymphocytes 12; large lymphocytes 7, large mononuclear cells 3, transitional cells 2, eosinophils 1, basophils 1; the red cells showed microcytosis. The Wassermann reaction was negative. The blood chemistry findings were: urea 30.2 mg., urea nitrogen 14.1 mg., creatinine 1.8 mg., sugar 0.115 Gm., uric acid 4.8 mg. per hundred cubic centimeters of blood.

Spinal fluid: The number of cells per cubic millimeter was 10. Globulin, Wassermann and colloidal gold tests were negative. Forty-eight hours after the specimen was submitted to the laboratory, the pathologist reported the discovery of yeast cells and requested a second specimen to rule out the possibility of contamination.

Urine: Color, clear amber; sediment, moderate; reaction, slightly acid; specific gravity, 1,020; albumin, a slight trace; indican, a moderate excess; many pus cells; few epithelial cells; few bacteria.

Course in the Hospital.—After admission to the institute the patient had no elevation of temperature. The lumbar puncture, which was done easily and with no particular discomfort to the patient, was followed by a severe reaction, and for the last five days in January the patient was noticeably weaker, and had nausea and vomiting practically every day. The patient attributed the gastric disturbance to medication but discontinuance of the drugs produced no change. Sleep was disturbed at night and the patient was drowsy during the day. Repeated questioning revealed no sleep disturbance previous to admission to the hospital, except when headache was severe. The condition of the patient did not permit a second examination of the spinal fluid.

Diagnosis.—The case was discussed at a staff meeting, Feb. 1, 1924. The general opinion was that the lesions were inflammatory and progressive, involving the oculomotor nuclei, with probably more widespread pathology than that clearly presented by the symptoms and signs. The conditions considered for differentiation were: epidemic encephalitis, chronic degenerative nuclear encephalitis, and brain tumor. Several members of the conference, including one of us (McKendree), considered epidemic encephalitis probable because of the oculomotor disturbances, headache, vomiting, sleep disturbance, and the laboratory findings of 10 lymphocytes in the spinal fluid. Another member believed that a chronic nuclear encephalitis of the degenerative type would explain best the picture. Brain neoplasm was ruled out by all because of the absence of signs of increased intracranial pressure, and the impossibility of producing these signs by an expanding lesion without the addition of signs attributable to pressure on structures adjacent to the oculomotor apparatus, either at the nuclei or in the course of the peripheral distribution of other cranial nerves. Dr. Frederick Tilney, however, emphasized the necessity of investigating further the findings of yeast cells in the spinal fluid and suggested that they might be the etiologic factor. He had recently observed a case of meningitis in which no yeast organisms were found in the first three punctures, but were later recovered in more than ninety successive punctures. The organism was a torula and caused the patient's death. This case was published by Shapiro and Neal.[2]

Unfortunately, our patient's condition was such that a second lumbar puncture could not be performed, and circumstances required that she be allowed to return to her home in another state two days later.

Subsequent Course.—Through the courtesy of Dr. James H. Kingman of Middletown, Conn., we were kept in touch with the clinical course from time to time, and on one occasion the patient was examined at the Middlesex Hospital, Middletown, Conn., by one of us (McKendree). For a time the nausea diminished in intensity, the ptosis improved somewhat, and the patient became quite comfortable and took food well.

March 14, 1924, there was a sudden collapse while the patient was confined to bed in the hospital. The pulse rate ranged from 110 to 120; the systolic blood pressure was 115 mm.; the rectal temperature rose suddenly to 101 F., and the pharyngeal muscles became weak, so that swallowing was difficult and mucus collected which was raised with difficulty. Ophthalmologic examination at this time revealed no abnormality.

There was steady and progressive involvement of the pharyngeal and lingual muscles; the patient could not swallow and had to be fed by tube. Facial paralysis was noted on one side and deafness became absolute. Some motion of the left

eye was noted and the facial paralysis became less marked as involvement of the medulla oblongata became more accentuated. The patient died, May 2, 1924, from involvement of the cardiac and respiratory centers.

Through the kindness of Dr. Jessie W. Fisher of Middletown, Conn., the brain was removed within a few hours and forwarded to us for study.[6]

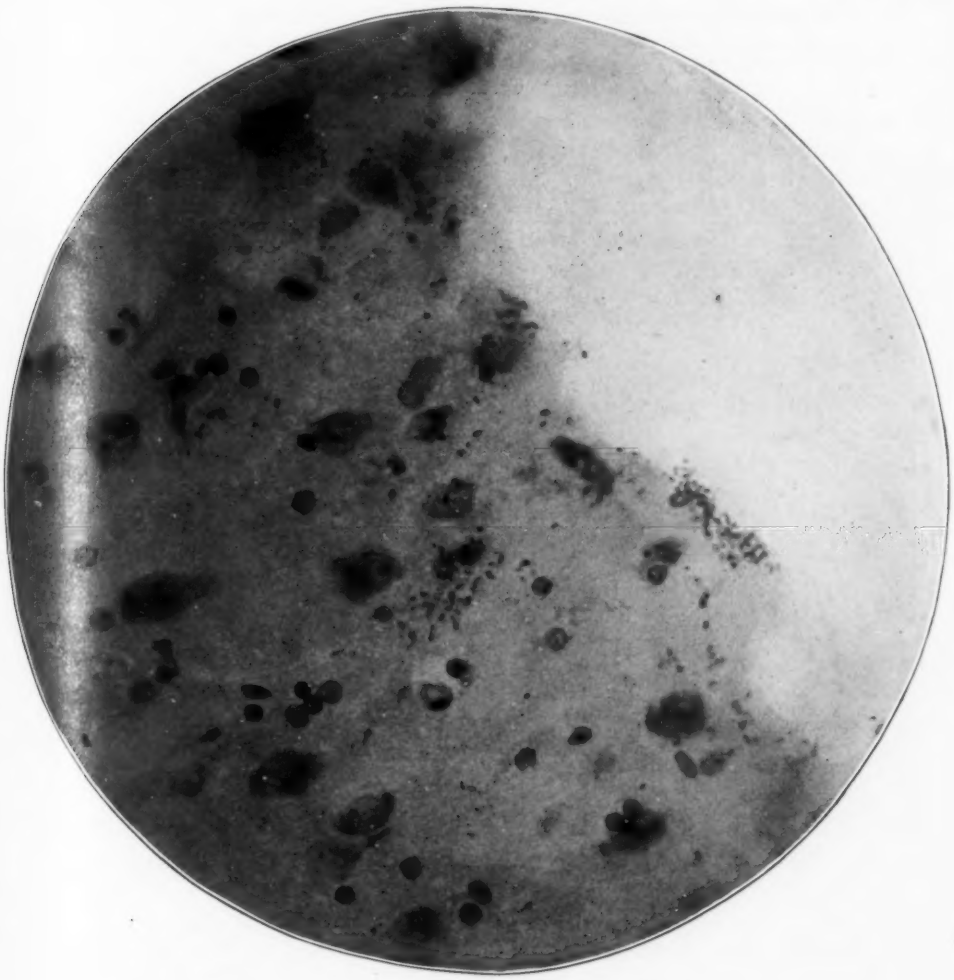

Fig. 1.—Low power photomicrograph of the left superior temporal convolution, showing organisms on the surface of the brain and in the cortex. Nissl stain.

GROSS PATHOLOGIC EXAMINATION

The brain was placed in a 10 per cent solution of liquor formaldehyde immediately after removal. It weighed 1,250 Gm. Measurements were as follows: fronto-occipital, 17 cm.; temporo-occipital, 14.9 cm.; biparietal, 13.5 cm.; bicerebellar, 10.9 cm. The general external conformation and symmetry were normal.

6. The study was made possible by a grant from the Commonwealth Fund.

There was intense venous engorgement of the pia-arachnoidal vessels, especially over the superolateral surfaces of both cerebral hemispheres. The leptomeninges of these regions were slightly opaque and milky in appearance. The basilar meninges had a similar appearance. No thickenings were noted in the basilar vessels. After removal of the pia mater the convolutions appeared normal, except for a very moderate flattening due to preservation.

The brain was sectioned macrotomically in a frontal plane beginning about 1 cm. posterior to the tips of the lateral ventricles into segments about 1 cm. in thickness. The differentiation between the cortical gray and the central white substance was well marked. The average measurement of the cortical gray was from 3.5 to 5 mm. The smaller blood vessels in both gray and white matter were abnormally injected. This feature was noted especially in the pons. The venae terminales were especially prominent. No areas of discoloration, necrosis

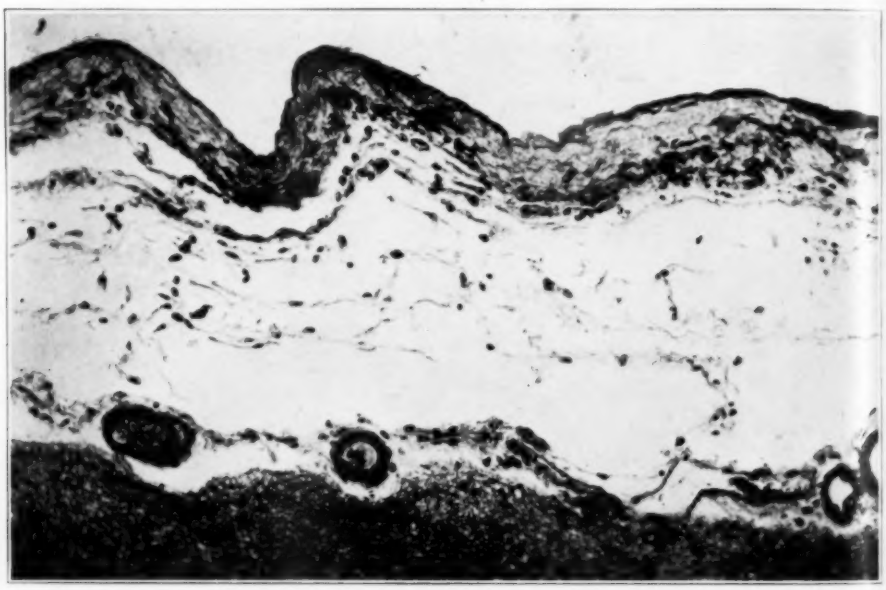

Fig. 2.—Low power photomicrograph of the left temporal cortex, showing the thickening of the arachnoid, with moderate cellular infiltration and edema of the pia-arachnoid. Hematoxylin-eosin stain.

or cyst formation were seen in any of the sections. The lateral ventricles were not distended, but the ependyma had a fine granular, sandpaper-like appearance.

MICROSCOPIC EXAMINATION

Within a few days after removal of the brain, two small pieces were taken for frozen section from the right superior frontal and the left superior temporal convolutions. They were stained with hematoxylin-eosin, Nissl's methylene blue, and scarlet red. The brain was then left in formaldehyde solution for about six months before study was commenced. Sections for microscopic examination were then taken from the following regions: right and left superior frontal gyri; left superior parietal cortex; right and left superior temporal convolutions; right striatum about 1 cm. from the cephalic extremity; right striopallidum; midbrain;

optic chiasm; pons (anterior, middle and posterior portions); medulla oblongata; cervical cord. The staining methods used were: hematoxylin-eosin, van Gieson, Mallory, Nissl's methylene blue, cresyl violet, Marchi, scarlet red and Pal-Weigert.

Meninges.—There was a chronic leptomeningitis of the convexity, base and lateral surfaces of the brain, which involved equally the cerebral hemispheres, temporosphenoidal lobes, midbrain, pons and cerebellum, and extended over the medulla and spinal cord.

In the frozen sections that were made first, round, oval and elliptical bodies, most of which stained well with the Nissl stain (fig. 1) were found in the

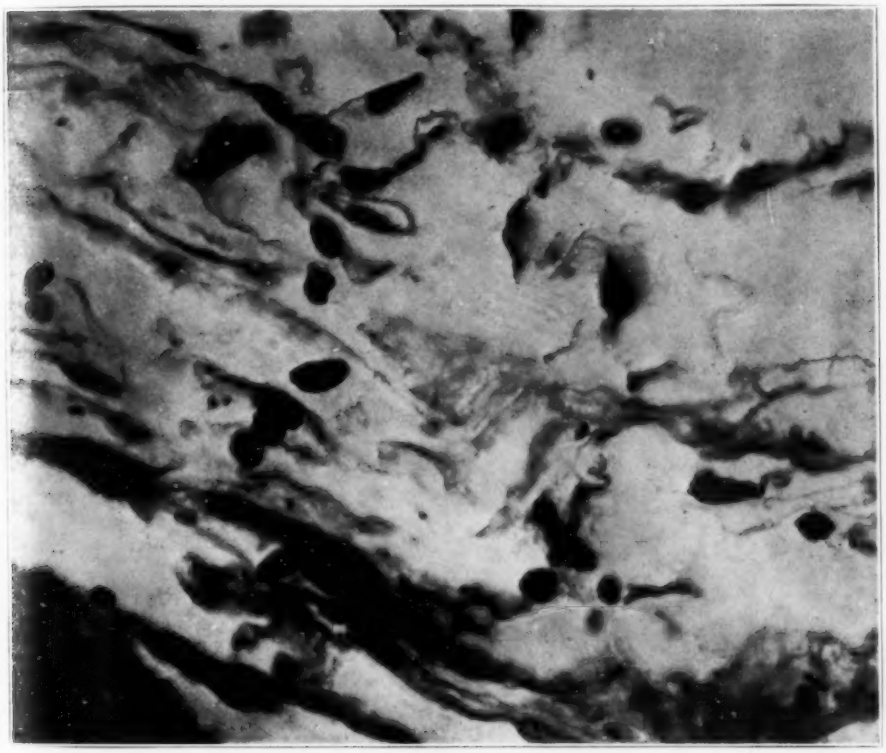

Fig. 3.—High power photomicrograph showing the appearance of the oval bodies with the threadlike projections in the pia-arachnoid. Hematoxylin-eosin stain.

meninges. They varied considerably in size and form, but in general were larger than lymphocytes, and were elliptical in shape with tapering ends which made their differentiation easy. A few forms appeared to be budding or to have recently divided. These were represented by cells of very different size either immediately adjacent to or actually in contact with each other. The smaller one was generally round and about one-third the size of the larger one; the latter was oval or elliptical. These cells stained homogeneously, some deeply and others faintly, and showed no differentiation into nucleus and cytoplasm. No forms with double contours were noted.

In the sections examined after prolonged fixation and celloidin embedding, great difficulty was encountered in distinguishing the parasites from inflammatory tissue cells, especially clasmatocytes.

The reaction in the meninges showed a considerable degree of variation. In certain areas the pia and arachnoid were widely separated by inflammatory edema, with only slight evidence of inflammatory exudation. In the areas in which this was noted the arachnoid was thickened. The central portion of the arachnoid was more faintly stained than the periphery and consisted of a more or less homogeneous substance having a wavy appearance. Nuclei were not so abundant in this central homogeneous zone as at the periphery, but delicate fibrillae were present. The outer and inner portions of the arachnoid were more dense, and the cells were disposed in one or more layers. The cells covering the arachnoid externally were flattened and elongated with ends tapering into threadlike pro-

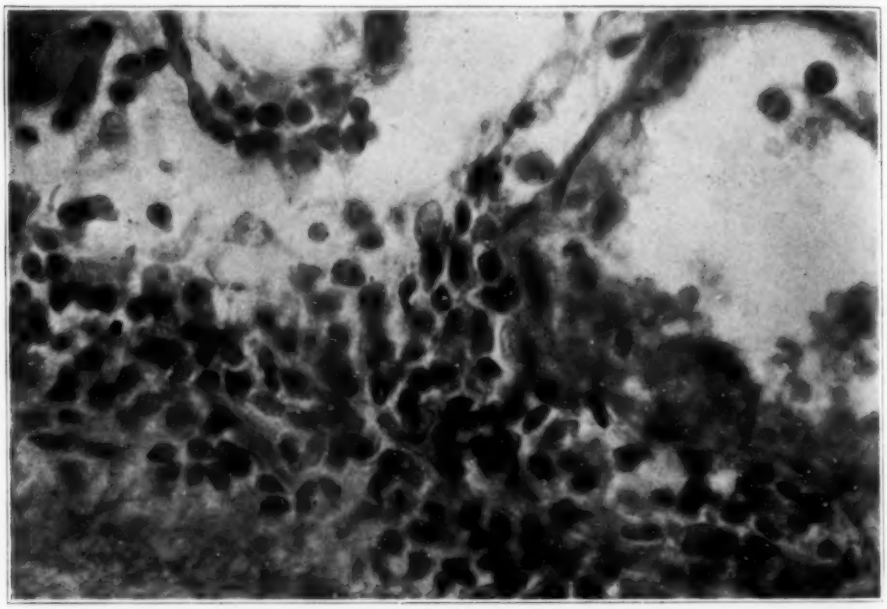

Fig. 4.—High power photomicrograph showing the infiltration beneath the pia mater and into the substance of the temporal cortex; the faintly stained oval and polyhedral forms may be noted. Hematoxylin-eosin stain.

longations (fig. 2). The nuclei were well stained. On the inner side of the arachnoid the cells were larger; the nuclei were mostly oval or oblong; they were faintly stained and contained chromatin granules. Some cells contained two nuclei. The protoplasm stained faintly and the individual cell margins were indistinct. These resembled endothelial cells. Among the trabeculae were many deeply stained cells with wavy threadlike protoplasmic projections resembling clasmatocytes (fig. 3). Occasionally, oblong oval and polyhedral forms were seen, some of which stained very faintly and others deeply. Some of them were surrounded by a hazy zone (fig. 4). Some of them we believe to be torulae although differentiation from tissue cells was difficult. Small nodules were encountered in the arachnoid; these were made up of clumps of faintly staining

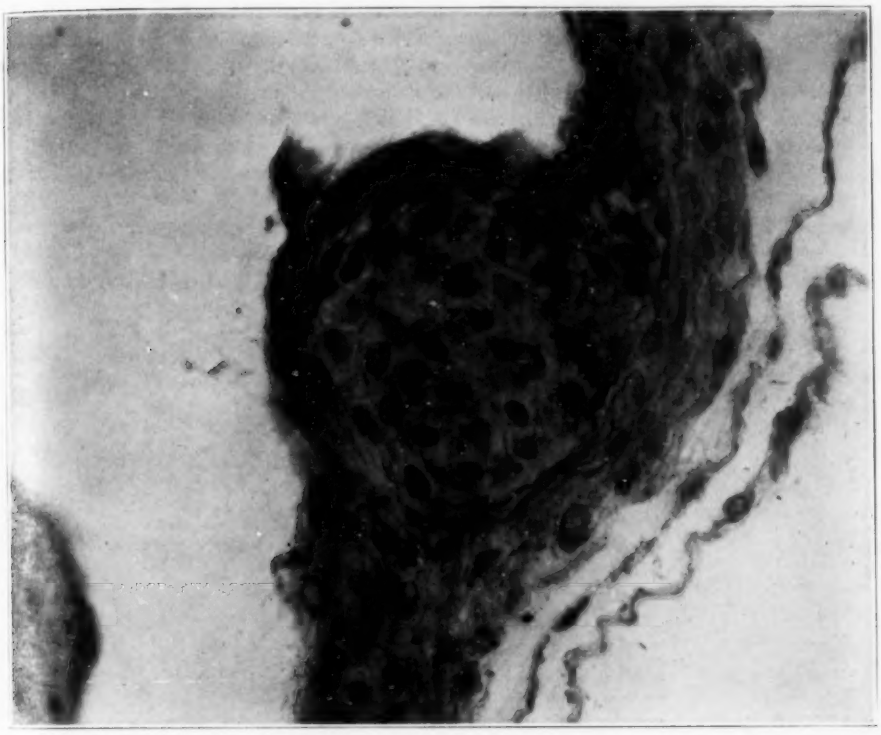

Fig. 5.—High power photomicrograph of a nodule from the arachnoid of the left superior frontal region. Hematoxylin-eosin stain.

Fig. 6.—Low power photomicrograph illustrating the infiltration of the pia mater and the adjacent cortex of the right temporal convolution. Hematoxylin-eosin stain.

bodies, not unlike endothelioid cell nuclei, and were embedded in a homogeneous substance with merely a suggestion, here and there, of cellular outlines. Some of these contained one or more deeply staining granules. At the periphery of these nodules the cells were elongated and the ends tapered into wavy threadlike prolongations. The nuclei were flattened and deeply stained (fig. 5). There was no central necrosis in any of these nodules, nor were they surrounded by lymphocytic infiltration. Giant cells were not noted. The formation of fibrous connective tissue was nowhere a prominent feature.

In certain areas the cellular reaction was the most striking feature of the picture. Where this occurred, the exudate was subarachnoidal, pial and subpial in location (fig. 6). The exudate consisted of lymphocytes, plasma cells and other

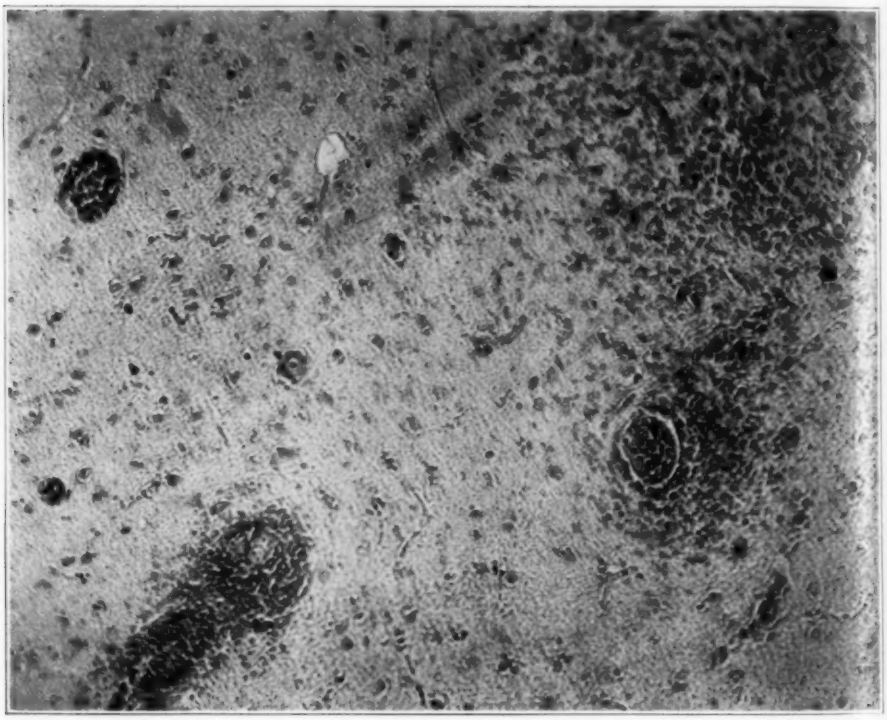

Fig. 7.—Low power photomicrograph showing the lesions in the right nucleus caudatus. Cresyl violet stain.

cells with faintly staining round and oval nuclei resembling endothelial or polyblastic cells. In this exudate were seen some forms with definite outlines, oval in shape, that stained faintly and were almost completely transparent except for the cell membrane. We concluded that these were torulae (fig. 4). The exudate extended into the cortical substance in many places.

Brain Tissue.—Cortical gray matter: There was an increase in the number of smaller blood vessels and a very marked proliferation of glia nuclei. The ganglion cells showed various types of degeneration including cloudy swelling, chromatolysis and fat pigment degeneration. Many of the large ganglion cells of the third, fourth, fifth and sixth laminae were almost completely filled with fat.

The most extensive degeneration of ganglion cells was in the fifth and sixth laminae of the temporal cortex. Here the satellite glia were arranged at the periphery and on the surface of the ganglion cells in groups of from three to ten. These glia cells consisted of small, round, pyknotic and fat granular types. Rod cells were practically absent from the picture except in the frontal cortex where one was occasionally seen. Many blood vessels were surrounded by zones in which the glia reticulum was loose and spongy in character. Fat was present in the walls of some blood vessels.

Central white matter: The glia cells in the white matter were very numerous and arranged in long rows between the nerve fibers. The Virchow-Robin spaces were greatly distended and densely packed with cells of endothelial or polyblastic character. The nuclei were hyperchromatic, contained a coarse chromatin network

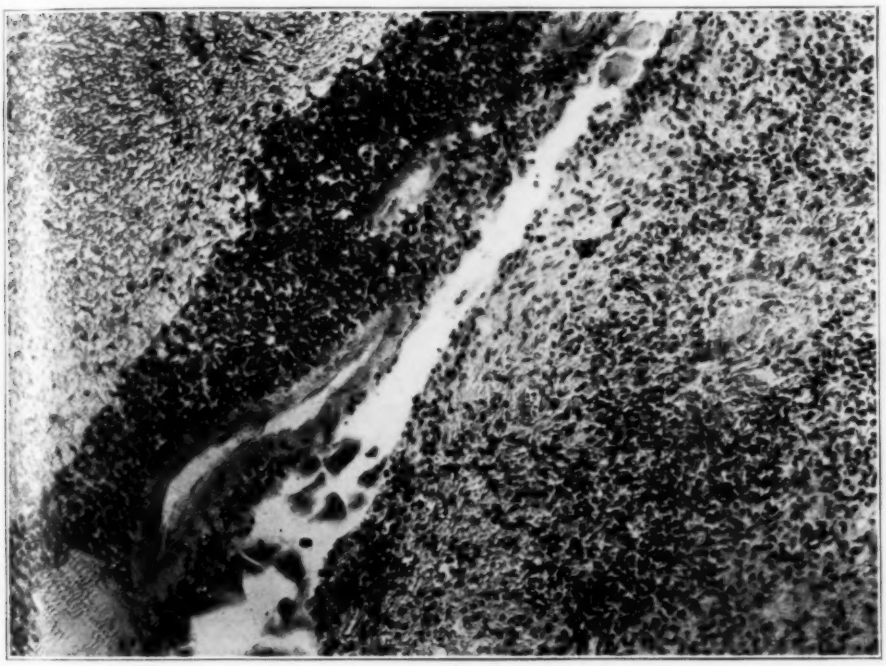

Fig. 8.—Low power photomicrograph showing the inflammatory reaction in the meninges covering the pons and extensive infiltration of the adjacent root of the fifth nerve. Hematoxylin-eosin stain.

and were polyhedral, oval and kidney shaped. Occasionally, however, there were seen some very large irregular shaped cells, from 20 to 30 microns in diameter, containing two or more large oval hypochromatic nuclei. A few lymphocytes and plasma cells were scattered among them but no polymorphonuclear cells were seen. Between the cells there was seen occasionally a clear space containing a small amount of faintly stained homogeneous material. The endothelial cells lining the blood vessels were swollen and the walls of some vessels were thickened. This thickened portion appeared homogeneous under low and medium magnification, but with the oil immersion long clear refractile bodies were seen encircling the vessels. Their outlines were distinct but the interior portions were clear and transparent.

Ependyma: The ependymal cells lining the ventricles and Sylvian aqueduct were swollen and stained with difficulty. Beneath the ependyma faintly stained globular bodies were seen. Whether these were parasites or altered nuclei could not be determined. Beneath the ependyma were nodular accumulations of large and faintly stained cells resembling those seen in the Virchow-Robin spaces already described. Mingled with these cells were proliferated glial elements. In places the ependymal cells were entirely lacking and the exudate extended into the cavity of the ventricle.

Corpus callosum: The perivascular infiltration was extreme and of the same type as that described in the centrum ovale. The glia cells were increased and there were areas of demyelinization, especially in the vicinity of the infiltrated areas.

Basal ganglia, substantia nigra and capsula interna: The perivascular lesions were extensive throughout the caudate, putamen, globus pallidus, optic thalamus,

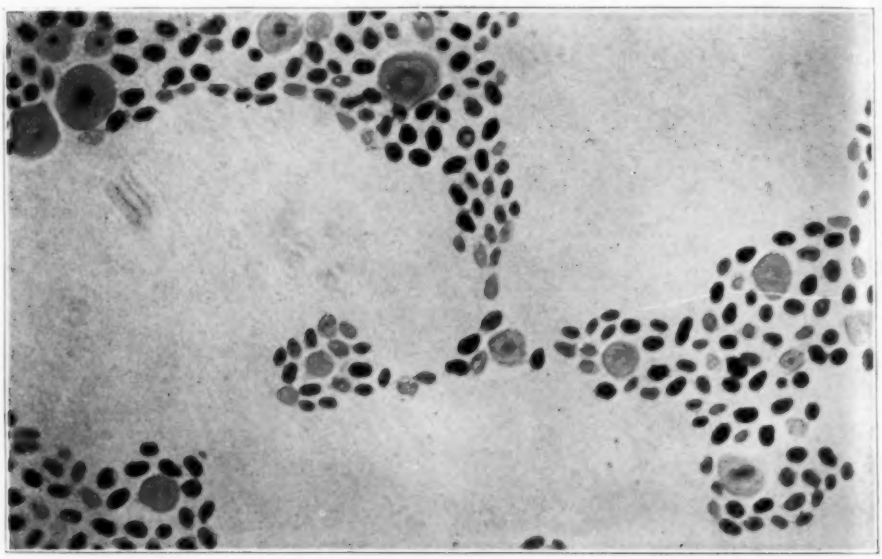

Fig. 9.—High power photomicrograph of some ordinary yeast cells after formaldehyde fixation and celloidin embedding; the variation in size, shape and staining reaction may be noted. Hematoxylin-eosin stain.

substantia nigra and internal capsule (fig. 7). Areas of diffuse infiltration at some distance from blood vessels were also present. The glia cells were increased. The ganglion cells were swollen, showed chromatolysis and were surrounded by satellite cells.

In the caudate and putamen, the degenerative changes appeared to involve about equally the large and small ganglion cells, possibly slightly more marked in the latter. Neurophagocytosis and satellitosis were everywhere apparent throughout the striatum, pallidum and optic thalamus. There was a marked proliferation of glia nuclei consisting of small round pyknotic forms probably representing microglia, larger forms probably representing oligodendroglia and protoplasmic glia, a few gitter cells and numerous rod cells. The latter were especially frequent in the pallidum.

Cranial nerve nuclei: The nuclei of all the cranial nerves showed degenerative changes in the ganglion cells characterized by swelling, eccentricity or complete loss of nuclei, transformation of the tigroid substance into fine dustlike particles, and in some cells complete disappearance of tigroid substance. The nerve roots were infiltrated with lymphocytes, plasma cells and polyblasts (fig. 8).

Pons: Perivascular lesions similar to those already described were present in the pons, and were most marked at the junction of basilar and tegmental portions. There was moderate demyelinization of the nerve fibers with nodular swellings. This was especially noticeable in the transverse fibers.

Cerebellum: Areas of perivascular infiltration were present in the molecular layer of the cerebellum. The Purkinje cells were quite well preserved, though some of them were swollen. The granular layer appeared normal.

SUMMARY

Without cultural studies it is impossible to identify with absolute certainty the parasite responsible for the extensive pathologic change in this case, but in view of the known tendency of torulae to produce lesions in the nervous system without skin manifestations, the slight tendency to the production of a gelatinous material in some of the lesions, and the complete absence of any suggestion of mycelia, endospores, abscesses, cysts or polymorphonucleocytosis, we believe we are warranted in the conclusion that the pathologic change was due to this organism.

The clinical and pathologic features of this case warrant its designation as subacute, progressive meningo-encephalitis, due to torula. All clinical signs and symptoms are readily explained by the pathologic findings. In conclusion, we wish to emphasize the urgent need of repeated careful cytologic and cultural studies in spinal fluid specimens, and of the inclusion of torula infection as one of the subacute inflammatory diseases of the central nervous system.

THE TREATMENT OF GENERAL PARALYSIS BY INOCULATION WITH MALARIA

A SECOND REPORT *

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AND
GEORGE H. KIRBY, M.D.
NEW YORK

The purpose of this second communication on the treatment of general paralysis by inoculation with tertian malaria is less a purely statistical review of the additional cases treated since the date of our first report [1] than it is a more detailed discussion than was then possible of certain features of the treatment as these have been exemplified in the case records of some of our patients. Certain of these observations are of the greater significance in view of the fact that some of the patients to be discussed have now been under observation for more than two years since the treatment was completed.

Concerning the malarial infection itself we have little to add. In the great majority of cases we have noted the occurrence of the "initial fever" referred to by Korteweg [2] and by Pieper and Russell,[3] which the latter have described as "a continuous fever, sometimes showing remissions or even more or less complete intermissions; lasting three or four days, and sometimes separated from the regular paroxysms which come on later by an interval which is free from fever." [3] A fever of this type has been present, even though with variable intensity and especially of variable duration, in twenty-one of twenty-four cases of our series in which particular attention was paid to this point. On the other hand, "relapses and cases which are infected a second time do not show this initial fever"; and while we have but one relapse to record (which conformed perfectly to this dictum), two of the patients who failed to exhibit an initial fever were both inoculated but not infected a second time, for in both the first inoculation had been unsuccessful. In one of these two patients the second inoculation was followed within forty-eight hours by a definite malarial paroxysm;

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* From the New York State Psychiatric Institute, Ward's Island, N. Y.

1. Bunker, H. A., Jr., and Kirby, G. H.: The Treatment of General Paralysis by Inoculation with Malaria: A First Report, J. A. M. A. **84**:563 (Feb. 21) 1925.

2. Korteweg, P. C.: De Aanfangskoorts der Malaria tertiana, Nederl. Tijdschr. v. Geneesk. **68**:1622 (April 12) 1924.

3. Pieper, A., and Russell, E. D.: Observations on Inoculated Malaria, South African M. Rec. **23**:178 (May 9) 1925.

and this abbreviated interval (instead of the usual period of five days or more) has been our almost invariable observation in those patients who have been inoculated a second time, after the first inoculation had been seemingly entirely without effect. In the other case, however, the incubation period was of the usual length; while at the same time, it should be added, the fever which then came on was intermediate in character between a definite "initial fever" and an obvious malarial paroxysm.

Of the spontaneous cessation of the febrile paroxysms there is only scanty mention in the literature, so far as we are aware. Yorke and Macfie,[4] it is true, observed this to occur in four patients of ninety-eight, and Pieper and Russell noted among their cases twenty-two instances of spontaneous termination of the infection; but we should consider it not without some bearing that in four of these writers' twenty-two patients, from seventeen to twenty-three febrile paroxysms had occurred prior to their failure to reappear, while in only three did the termination of the infection come about earlier than the eighth paroxysm. In 118 patients we have observed what appeared to be a spontaneous "cure" of the infection in fourteen, this statement being based on periods of freedom from pyrexia subsequent to the final paroxysm which ranged from four days (one case) to eleven to sixteen days or longer (six cases); and we might perhaps include three additional patients whose paroxysms were becoming progressively and conspicuously less severe but to whom quinine was given after only two days of freedom from fever. In these fourteen patients the apparent dying out of the infection took place after one (one case), five (four cases), six (three cases), seven (one case), nine (three cases), ten and twelve (one case each) paroxysms, respectively. But it is also to be noted that in five cases there occurred, subsequent to the fourth paroxysm, a protracted interval of from five to eleven days between one attack of malaria and the next, after which the paroxysms succeeded each other with regularity and with undiminished intensity.

As others have reported, the incubation period—the interval between (intravenous) inoculation and the first definite malarial paroxysm—has undergone no change in length with successive passages of the inoculum from host to host. From five to seven days, rather more frequently the former, remains the interval most commonly occurring; very occasionally the period has been nine days; in three patients only the interval has been eleven days. An abbreviated incubation period of two days or even less has been almost invariably encountered in the

4. Yorke, W., and Macfie, J. W. S.: Observations on Malaria Made During Treatment of General Paralysis, Tr. Roy. Soc. Trop. Med. & Hyg. **18**:13 (March 20 and May 15) 1924.

case of a second inoculation, given when the first had failed to produce infection; an incubation period of three days or less has been seen only occasionally in nonreinoculated patients. On the other hand, when the first inoculation has produced an actual infection, a second inoculation has been followed by an incubation period of ordinary duration.

Of 120 patients, only eleven (exclusive of negroes) failed to become infected at the first (intravenous) inoculation (Yorke and Macfie report five such cases of 70); three of these eleven had had a course of malaria six months before, although other previously treated patients responded successfully to the first inoculation on the second occasion. Only one of these nine (two patients were not reinoculated) failed to become infected on reinoculation; this patient was inoculated four times in all (each time simultaneously with a successfully inoculated patient); six days after the fourth inoculation he had but a single chill and rise of temperature (to 103 F.), without subsequent pyrexia during a period of four weeks.

Certain observations regarding "immunity" in malaria will be reported elsewhere,[5] and the same statement applies to the matter of increments and decrements of body weight in connection with the malaria treatment,[6] and to the influence of the treatment on the spinal fluid picture;[7] so that we may here pass to a consideration of our actual case material.

During the period June 1, 1923, to March 15, 1926, the total number of male patients, with few exceptions having undoubted cases of general paralysis, who have been inoculated with tertian malaria is 129—the last two patients inoculated representing the fifty-fourth successive passage from host to host of the strain of plasmodium which has been in use since Sept. 15, 1923. Among these 129 patients, five who were subjected to a second course of malaria some six months after the first are counted twice, and three died subsequent to inoculation but prior to a malarial paroxysm; we subtract also one certain and three probable cases of cerebral syphilis with psychosis, and one case of juvenile general paralysis; so that 116 cases remain. Of these, the number of patients in whom the period which has elapsed since the completion of treatment has been sufficient to permit a reasonably definite decision regarding the clinical result obtained is 106 (table 1).

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5. Bunker, H. A., Jr.; Fiertz, C. O., and Hinsie, L. E.: A Note on Inoculation Malaria in Negroes, to be published.

6. Bunker, H. A., Jr.: The Significance of Gain in Weight in the Malaria Treatment of General Paralysis, Arch. Neurol. & Psychiat., to be published.

7. Kirby, G. H.: The Effect of Malaria on the Spinal Fluid Findings in General Paralysis, to be published.

The five groups (table 1) will be considered seriatim, with illustrative case material.

FATAL CASES

The twenty-two patients in this series who died fall logically into two categories: those whose death occurred during the actual course of malaria or within a few weeks thereafter (thirteen cases), and those in whom death did not take place for a number of months after the completion of the treatment (nine cases).

Of the thirteen patients in the first group, six died at an interval of from one to six weeks after the final malarial paroxysm. In two of these, neither of which came to necropsy, death took place from inanition, occurring one week and six weeks, respectively, subsequent to the completion of the course of malaria; both these patients were very poor physical risks from the beginning. A third, a violently manic patient, died of exhaustion ten days after the final attack of malaria. On account

TABLE 1.—*Results in One Hundred and Six Cases*

		Number	Per Cent
Died		22	20.8
During or immediately following malaria	13		
Subsequently (after from 2 to 11 months)	9		
Unimproved		26	24.5
Slightly improved		8	7.5
Moderate remissions		13	12.3
Good remissions		37	34.9
Total		106	100.0

of his mental status he too might have been considered a poor physical risk, for he had lost at least 20 pounds (9 Kg.) in weight prior to admission to the hospital and an additional 10 pounds (4.5 Kg.) in the seven weeks before inoculation; rather curiously, however, he lost no weight whatever during the course of the malaria, but lost 6 pounds (3 Kg.) during the last week of his life, dying of exhaustion and toxemia secondary to decubitus. The fourth patient was known to have a quiescent pulmonary tuberculosis; he constitutes a warning in that the malaria apparently stirred this into activity, so that he died of this condition, as shown at necropsy, four weeks after his final attack of malaria. The fifth patient died suddenly two weeks after completing the course of malaria; there was no reason to suppose that he would not withstand the treatment, and since necropsy was not performed the precise cause of death cannot be stated. The sixth patient had a history of three previous convulsive seizures, which occurred five months, forty days and thirty-seven days, respectively, prior to inoculation with malaria. On the twelfth day following the completion of treatment he had a series of twenty-two convulsions which resulted in death.

In sum, then, a fatal outcome was undoubtedly hastened, even if not directly caused, by the malaria treatment in three of these six patients, all three of whom were poorly selected, at best, for this form of therapy; in one, the actual rôle of the malaria in the patient's demise cannot be stated; the two remaining patients would undoubtedly have died in any event, and the malaria did little or nothing to accelerate their end.

But the seven patients who died during the actual febrile period naturally present a somewhat different picture. The direct cause of death in two of these was convulsions, which occurred during the first definite access of temperature in one case, and during the second in the other. One of these patients had a history of two attacks of unconsciousness fifteen and ten months, and a series of convulsive seizures two months, prior to inoculation. The other patient, who succumbed during his second malarial paroxysm, had no history of this kind; but it is interesting, though probably irrelevant, that seventeen years ago he had, for a period of six years beginning at the age of 19 or 20, a number of epileptiform seizures at intervals of from three to six months, which had not recurred since. Other patients, with or without a history of previous convulsions, have developed seizures during the course of the malaria, although without a fatal outcome; these instances cannot, however, be discussed in this place. Of the remaining five patients, two died of pneumonia following the fifth and ninth malarial paroxysms, respectively; such, at any rate, was the clinical appearance, since neither case came to necropsy. The fifth patient in this group died suddenly on the day following the seventh attack of malaria, no definite cause, in the absence of necropsy, being ascertainable. The death of the sixth patient was associated with a rather profuse hemorrhage from the bowel which took place during the fourth febrile paroxysm. A similar complication characterized the final week of life of one of the patients already referred to who died of inanition; intestinal hemorrhage occurred also in a patient recently treated, without death ensuing, however; and it was likewise associated with the death of a general paralytic woman not included in the present series. In the seventh patient, death took place almost with the first appearance of the "initial fever"; at necropsy he showed little of an abnormal character beyond a distinctly fibrous condition of the myocardium, so that death may have been attributable to "heart failure," which, indeed, may have been the cause in two of the patients cited, and perhaps in a third, whose sudden demise was not satisfactorily explained.

These thirteen cases have been cited in such detail as has been possible for the reason that, since the malaria itself appears to have been at least the indirect cause of death in eleven (if we include, that is, the

patients whose fatal convulsions occurred in direct relation to the febrile period, but not the patient in whom they occurred at some interval afterward), it is evident that the treatment is not altogether devoid of risk even in more carefully selected cases than were some of these. At the same time, we have not encountered complications and contraindications in the variety referred to, for example, by Reese and Peter.[8] On the other hand, in contradistinction to Gerstmann's seeming opinion,[9] we feel obliged provisionally to specify a history of previous convulsive seizures, not as a definite contraindication to the malaria treatment, but certainly as a feature which should be recognized by all concerned as considerably increasing the possibility of an unfavorable outcome.

The nine patients whose death occurred some months after the completion of the malarial treatment, and had, therefore, nothing to do with the treatment itself, form the group which represents the minimum of therapeutic result, obviously, and a group to which, as time goes on, will undoubtedly be added some of the "unimproved" cases and very possibly others.

These patients died at intervals of from two to eleven months after the completion of treatment, the average period being six and one-half months. In only two instances could the patient be said to have pursued a consistently downward course from the time the febrile period terminated; in four the mental condition of the patient appeared to remain essentially stationary until only two or three weeks prior to death; in three cases, two of which were well advanced at admission, there even occurred a definite mental improvement which lasted six weeks in each case, followed, however, by a rapid decline and death within three months.

UNIMPROVED CASES

The unimproved cases are chiefly of interest because implicit in the cases that show little or no improvement in consequence of the malaria treatment is the problem of the factor or factors responsible for this minimal or negative result. It seems safe to suppose that one of these factors, operative in perhaps the majority of cases if not necessarily in all, resides in whether or not sufficient structural damage had already taken place at the time when treatment was instituted to preclude the possibility of partial or complete functional restitution such as is observed in more successful cases. But we have no criterion during life of the severity or character of such damage, for this is not necessarily corre-

8. Reese, H., and Peter, K.: Die Einwirkung der Malaria tertiana auf die progressive Paralyse, Med. Klin. **20**:372 and 410 (March 23 and 30) 1924.

9. Gerstmann, J.: Die Malaria-Behandlung der progressiven Paralyse, Berlin, Julius Springer, 1925, pp. 86, 101 and 103.

lated with the duration of actual symptoms, as Alzheimer,[10] Jakob[11] and others have long since pointed out, nor is it deducible, in many instances, from the character or intensity of the mental symptoms. It is accordingly not surprising that patients who (judged on the basis simply of the duration of mental symptoms—of clinical general paralysis) offer no expectation of a completely favorable response to the malaria treatment, nevertheless sometimes do so respond; while it is certainly equally true that other patients achieve a therapeutic result which is very disappointing in the light of the relatively brief period during which they have been victims of clinical general paralysis. Nevertheless, the undoubted importance of the extent and character of the anatomic changes already induced in the brain at the time of the inception of treatment, unfortunate though it may also be that we possess no accurate clinical criteria for their evaluation, does not preclude the possibility, in our opinion, that the failure to obtain a relative therapeutic success may be due in some cases not so much to the irreparable character of the cerebral changes present, as to the fact that the malaria treatment has in such cases failed to call forth an adequate reaction on the part of the organism. If such an interpretation is correct, these twenty-six patients in whom no particular degree of mental improvement is to be recorded owe the failure to one or both of these two possible factors, the presence of either of which must render nugatory the absence of the other.

What an adequate reaction on the part of the organism consists of, however, is difficult to express in concrete terms, for of its nature and of the criteria for its estimate we have no real inkling. We know only that patients who "respond" to therapy of this type, whether it be the malaria treatment or some other form of foreign protein therapy, manifest the response not infrequently by an increased sense of well-being,[12] by a gain in weight,[13] and by transitory alterations in the leukocyte

10. Alzheimer, A.: Ergebnisse auf dem Gebiete der pathologischen Histologie der Geistesstörungen: I. Die progressive Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **5**:754, 1912.

11. Jakob, A.: Zur Klinik und pathologischen Anatomie der stationären Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **54**:117, 1920.

12. Weichardt, W.: Ueber unspezifische Leistungssteigerungen (Protoplasmaaktivierung), München. med. Wchnschr. **67**:91 (Jan. 23) 1920.

13. Bunker (footnote 6). Boeck, E.: Versuche über die Einwirkung künstlich erzeugten Fiebers bei Psychosen, Jahrb. f. Psychiat. **14**:199, 1896. Uddgren, G.: Einige Erfahrungen über die therapeutische und diagnostische Bedeutung der Milchinjektionen, besonders in der Ophthalmologie, Stockholm, I. Haeggström, 1918, pp. 121 and 122.

count,[14] in certain ferments of the blood [15] and, it is said, in the permeability of the capillaries.[16] We are not justified in discussing further at this time a conception of a perhaps purely theoretical character, while it would at the same time be premature to refer in too forthright a way to the suggestions derived from our own material which seem to us to point to some humoral factor of this general nature. Let us say only that we have been at times unable to escape the impression that a satisfactory outcome in the treatment of general paralysis may depend, not only on the absence of irreparable and irrecoverable anatomic changes, but also on the capacity of the organism to react to the stimulation which the malaria treatment, as apparently a form of foreign protein therapy, is potentially capable of furnishing: the absence of such response rendering impossible, in certain cases, the mental improvement which organic damage alone might not have precluded, to judge at any rate by the example of the slightly and moderately improved cases in which a definite "response" to the treatment appears to occur and only organic damage already brought about seemingly stands in the way of mental recovery of the degree which could be considered a full remission. And while it is true that no present criterion exists whereby to prove the existence of this supposed reactive response, much less to measure it, we have come to feel provisionally that the phenomenon of gain in weight following the malaria treatment contains, perhaps, a suggestion of this order. For it has seemed to us suggestive that with reference to a posttreatment gain in weight the moderately improved and even some of the slightly improved cases are not only quite comparable to the fully improved, but stand in marked contrast, in this respect, to the unimproved cases [6]—as though much of this contrast were an expression of the presence or absence of "reactive response," while the various degrees of mental improvement were correlated, rather, with the extent of the anatomic brain changes. At all events, hypothetic as the notion of a "reactive response" may be, to reject it outright would necessitate the proof that not alone in a few cases, but in all cases, the therapeutic outcome hinged solely on the degree of anatomic cerebral damage present—a consideration not only insusceptible of present proof, but also (with due regard for the fact that history and symptomatology supply little real help) *a priori* improbable.

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14. Bunker, H. A., Jr.: Hourly Leukocyte Counts in Malaria, as Observed in Malaria-Treated Cases of General Paralysis, to be published.

15. Petersen, W. F.: Serum Changes Following Protein "Shock" Therapy, Arch. Int. Med. **20**:716 (Nov.) 1917.

16. Luithlen, F.: Ueber die Einwirkung parenteral eingeführter Kolloide und wiederholter Aderlässe auf die Durchlässigkeit der Gefasse, Med. Klin. **9**:1713, 1913. Starkenstein, E.: Proteinkörpertherapie und Entzündungshemmung, München. med. Wchnschr. **66**:205, 1919.

We will cite here a case that ran a very varied course and that may serve to illustrate some of the foregoing considerations.

REPORT OF CASES

Case 1.—G. F. S., a mounted policeman, aged 43, on admission to the hospital April 26, 1924, was single and lived with his father, who, although a man of moderate intelligence, had observed no abnormality in his son prior to the middle of March, some six weeks prior to admission. This earliest observed change took the form of the patient's neglecting to put away tools with which he was working on his car, according to his strict custom. About April 1, he conceived the idea of replacing the wheels of his car with disk wheels; he immediately acted on the idea and made the change in person, but it took him eight hours to carry it out. Within the next two weeks he was observed to drive his car recklessly. He continued in his employment as a mounted traffic police officer until April 22.

Examination.—On admission he was distractible and incoherent, restless, untidy in appearance, irritable at times, euphoric and expansive. The pupils were irregular and unequal, and reacted sluggishly to light; there was slight ptosis of the left upper eyelid. On two examinations the spinal fluid showed 85 and 72 cells; the Wassermann reaction was + + + + with 0.2 cc., and there was a strongly general paralytic type of gold curve.

Treatment and Course.—The man was inoculated with malarial blood, May 17, 1924. Nine malarial paroxysms occurred between May 24 and June 9. He lost only one-half pound in weight during this period.

By the end of July, some six weeks after the final attack of malaria, he showed considerable improvement. He had lost all but a suggestion of his former irrational behavior and ideas, and had even acquired a moderate degree of insight. He had gained 18½ pounds (8 Kg.) in weight. The cell count in the spinal fluid had not returned to normal, however, as we have almost invariably observed it to do in the immediate wake of the malaria treatment. Although a week after the final febrile paroxysm the cells numbered only 16, three weeks later (July 8) they were 27, and two months later (September 2) 120 in each cubic millimeter; September 23, October 7 and October 21, the cell count was 80, 77 and 80, respectively. We refer to this because we have come to regard as of bad omen the persistence of pleocytosis after the completion of treatment.

Until the middle of November, a period of four months, the man continued in a moderate remission, exhibiting as a residuum of his mental disorder only a certain childishness in general attitude, together with a very mild degree of euphoria and some tendency to occasional irritability; in spite of this the improvement in his mental status as a whole was rather striking. Throughout almost this entire period he maintained, but did not exceed, the original gain of 18 pounds in weight which he had registered within the first four weeks of his final attack of malaria.

From about the middle of November, however, a definite falling-off began to be apparent, becoming conspicuous during the ensuing month. He became increasingly silly and childish in his talk and behavior, and also more elated; in particular, he became excitable, irritable, impulsive and quarrelsome. It is interesting that a very gradual loss of weight began to take place as early as the middle of October, although by the first of January this loss had amounted to only 9 pounds (4 Kg.). Marked pleocytosis continued undiminished; on four occasions between November 11 and December 30 the cell count ranged from 32 to 109. The Wassermann reaction, colloidal gold test and globulin remained entirely unchanged.

Jan. 7, 1925, the man was again inoculated with malaria, one of the few patients in our series to repeat the malaria treatment. Between January 7 and 24 he lost 12 pounds (5 Kg.) in weight, and so reached a level practically identical with that at the end of his first course of malaria, June 10, 1924. Throughout the ensuing two months he was extremely disturbed, boastful, quarrelsome and assaultive; he entertained active delusions of having murdered relatives and others, together with bizarre ideas of a somatic character; an affect of anxiety was much in evidence; he appeared frequently to react to auditory hallucinations.[17] From this time onward he slowly grew increasingly demented. At no time subsequent to completing the second course of malaria did he gain in weight, as he had so conspicuously following the first course; he lost progressively instead, so that by Nov. 10, 1925, he was 16 pounds (7 Kg.) under the weight at the time of completing treatment (Jan. 24, 1925), 28 pounds (13 Kg.) under the weight immediately prior to his second inoculation (Jan. 7, 1925) and 17 pounds (8 Kg.) under the admission weight (May 2, 1924). The spinal fluid picture remained unchanged and the cell count much elevated, although on Nov. 10, 1925, the latter was only 13 per cubic millimeter. He died, Dec. 11, 1925, after a series of convulsions.

We here appear to have two types of therapeutic response in the same patient, and this with an intervening period of only about five months, during which it seems doubtful if the anatomic process could have advanced to a sufficient degree to account in itself alone for the extreme difference in the two experiences, especially since much of the five months in question was characterized by a distinctly favorable reaction which it is difficult to imagine could go hand in hand with a marked advance of the pathologic process. If it is true, moreover, that in gain in weight we have one manifestation of the response per se to the malaria treatment, then there could be no greater contrast than between the behavior of the weight curve after the first course of malaria and that after the second.

Only five other patients in this series have been subjected to two courses of malaria. None of these derived any appreciable benefit from the first course; four of them derived none from the second. The fifth, however, exhibited after the second course so much better an adjustment to institutional life as to entitle him to be classified as "slightly improved"; while pari passu with this by no means conspicuous improvement a marked gain in weight took place, very much the opposite of the tendency which he had evidenced throughout the three months subsequent to the first course of malaria.

Before passing to the cases in which a better therapeutic result was obtained, we will cite what must be a rather unusual reaction occurring in a patient who is now classified among the unimproved, but who was at one time regarded as presenting a moderate if not complete remission.

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17. Gerstmann, J.: Zur Frage der Umwandlung des klinischen Bildes der Paralyse in eine halluzinatorish-paranoide Erscheinungsform im Gefolge der Malariaimpfbehandlung, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:200, 1924.

CASE 2.—P. A., a bricklayer, aged 45, was admitted June 21, 1924, having complained for the preceding six months of frequent dizziness, although it was also stated that for some years he had made an occasional complaint of a similar nature. For about the same period a rather marked degree of irritability had been noted in the patient, which was, in fact, a considerable exaggeration of a tendency normal to him. One week prior to admission he became, with great suddenness, extremely irrational, expansive, voluble, hyperactive and sleepless. On admission he was restless, noisy, irritable, querulous, talkative, at times assaultive, and extremely euphoric. The pupils were very unequal in size and did not react at all to light. He appeared to be a particularly favorable patient for treatment because: (1) he presented a "manic" type of general paralysis; (2) the outbreak of frank mental symptoms was extremely recent, and (3) there was a relatively brief prodromal period preceding this.

Treatment and Course.—The man was inoculated with malarial blood, July 17, 1924, and completed his course of treatment (nine paroxysms) July 30.

It was three weeks before the patient began to show any improvement whatever; but at the end of a little over three months (early in November, 1924) he had attained a very satisfactory remission on the whole, characterized by a fairly complete degree of insight, an unusually accurate retention and reproduction of everything that had taken place since admission, but, on the other hand, a certain slowness and dulness of apprehension. By this time he had come to weigh 16 pounds (7 Kg.) more than he had immediately before inoculation—a gain of nearly 20 per cent of his pretreatment weight. Although in our experience insight is more often than not the last indication of improvement to make its appearance, in this patient the last mental symptom to disappear was certain of his former grandiose ideas which for some time recurred occasionally, to his annoyance, since he had fairly good though somewhat wavering insight into their abnormal character. He was discharged, Dec. 19, 1924, four and one-half months subsequent to the final attack of malaria.

Six weeks later, Jan. 29, 1925, the patient was returned to the hospital. At home his behavior had been in all respects rational; but about a month after his discharge he began to complain of what he called a buzzing in the head (perhaps quite similar to his complaint of "dizziness" of the preceding spring) which he referred chiefly to the left side of the head, and which troubled him especially at night. While none of his former psychotic symptoms whatever had been in evidence, he began to express a fear that he would die on account of these noises—that he would never get over them. He had lost no weight since discharge.

After readmission to the hospital he rapidly developed a mental picture essentially typical of an anxious depression with hypochondriacal delusions. At the same time he preserved his former fairly complete insight into the earlier psychotic episode, without, of course, any insight into the mental disorder which had since appeared. In no other case to date have we observed a situation of this striking character—a practically complete recovery, that is, from the earlier mental manifestations of general paralysis (psychomotor overactivity with delusions of grandeur), and its subsequent replacement by a different mental picture (anxious depression with a hypochondriacal trend); although it is possible that we have here a special instance of the general phenomenon occasionally observed in general paralysis in which the patient pursues a circular course, clinically indistinguishable from the circular form of manic-depressive psychosis.

His state of depressive anxiety has not changed materially during the past eleven months. The Wassermann reaction in the blood has remained ++++. One year after the completion of treatment (August 18 to November 2) the

Wassermann reaction in the spinal fluid became negative in 0.15 cc., but remained + + + + in 0.4 cc. A general paralytic type of colloidal gold curve has never been present; it was: once, immediately after the malaria, as nearly general paralytic as 3443332100; three times, of the syphilitic type; on four occasions negative.

In general, it has been our experience with regard to the "unimproved" cases that the mental condition remains essentially unchanged for a considerable time after treatment has been completed—long enough in many instances to give rise to the impression that treatment has served to arrest the disease *in statu quo ante,* although a lapse of time much greater than two years will be necessary to make this certain. In a few patients this supposed "arrest" is temporary, and the patient becomes definitely worse, or dies, after three months or more during which the clinical condition appears to be essentially stationary. In a few cases, the "arrest" does not take place at all, and the disease appears to advance, after a brief interval or none at all, as it might have done if the patient had remained untreated.

SLIGHTLY IMPROVED CASES

In this somewhat artificial category are placed only eight patients—those who have shown a distinctly improved institutional adaptation, or who have, shortly after treatment, conspicuously "braced up" from a state of marked dementia and dulness, yet who could not possibly be classed, because they are still obviously general paralytic patients, among the patients exhibiting even moderate remissions. From the mental standpoint they seem obviously allied to the unimproved cases; yet, as has been pointed out elsewhere,[6] when they are regarded from the standpoint of gain in weight following treatment, they appear to stand in closer relationship, on the whole, to the moderate and full remissions, for the gain in weight registered during the first three to six months of the posttreatment period is at least comparable, in at any rate these few cases, to that recorded by the patients whose mental improvement is much more marked.

MODERATE REMISSIONS

This group is of interest in that many of its members fall not very far short of fairly complete remissions, while from the standpoint of posttreatment gain in weight they are, on the whole, entirely comparable to the latter. Three of the thirteen patients in this group, indeed, lack only the crucial test of an attempt to resume their former occupations for a decision as to whether they are not really examples of fairly complete remissions, for they present very little which would *a priori* seem to make this test impossible of success. Yet a fourth patient, although he made an extremely good impression whenever interviewed, mani-

fested no definite defect symptoms and exhibited a very complete degree of insight, was a failure when he attempted to resume his former occupation, for his manual clumsiness alone interfered hopelessly with carrying out many of the procedures of his calling, that of a photographer; but in addition to this he exhibited a number of traits at home—such as unreliability—which were not in evidence while in the hospital. So that it is necessary to classify this patient as a moderate remission only, in spite of the rather high degree of preservation of his personality, absence of definite defect symptoms on the intellectual level and acquisition of a really complete degree of insight—a result actually much more remarkable than it appears at first sight, because of the long duration of clinical general paralysis (of the simple dementing type) before treatment was undertaken.

Three cases in this group will be briefly outlined:

REPORT OF CASES

Case 3.—G. F. had had definite symptoms of general paralysis of the simple dementing type for at least eight months prior to admission. During the febrile period of his malaria he had two slight convulsive seizures, having had no previous history of such episodes. He was slow in exhibiting improvement after treatment, and indeed his weight curve paralleled this delay so closely that at the end of three months (having lost considerable weight during the malaria) he weighed practically the same as he had at the time of inoculation, although three months later he had added 17 pounds (8 Kg.) to this. Eventually, however, he lost almost all of his previous very marked dulness and apathy, overcame to a rather surprising degree his earlier conspicuous retention and memory defect (for both remote and recent events), and gained a fair degree of insight; at the same time thinking, speech and especially bodily movements remained very much slowed. In this condition he left the hospital, but later found it impossible to keep a position as a waiter (his former occupation) because of his slowness. About three months after discharge he had two brief syncopal attacks, and he also began to exhibit an increased tendency to sleep; the latter had not been a characteristic of the first onset of general paralysis. The spinal fluid findings have undergone no improvement save for the cell count.

Case 4.—M. K. exhibited very few mental symptoms on admission except slight boastfulness, mild elation, rather marked irritability and complete absence of insight. Improvement following treatment was therefore not very dramatic; but he lost the euphoria and gained full insight, while his irritability, which was in no small measure a normal trait for him, became definitely modified. He was discharged and shortly entered the employ of an insurance company, which reported his work as very satisfactory. More than a year after leaving the hospital, however, he began to be excessively irritable at home, to make gross errors in his accounts resulting eventually in a considerable shortage of money, and to involve himself without apparent provocation in arguments and altercations with the clients of the company. All these things he denied stoutly and persistently, even when confronted with proof. At no time has there been any definite modification of the spinal fluid findings save with respect to the cell count.

CASE 5.—L. H., aged 37, entered the hospital May 17, 1924, after having manifested definite mental symptoms for six months and a state of marked hyperactivity accompanied by grandiose delusions for two months. During the latter half of June he underwent a course of malaria treatment (thirteen paroxysms in all), within a month of completing which he began to show a considerable degree of improvement; so that exactly three months from the date of the final attack of malaria it was possible to discharge him from the hospital, October 2. At this time all mental symptoms had disappeared and he had acquired a perfect degree of insight. At home, however, he displayed a lack of self-confidence as to his ability to resume his occupation as a piano tuner; he seemed to believe that there was something lacking in him which made this impossible. Otherwise nothing abnormal was noted by his relatives, save that he appeared unable to make a satisfactory adjustment to the fact that his wife continued to regard him as a source of possible infection and to show this plainly. After he had been at home for nearly two months, the failure of an attempt to obtain work appeared to depress him noticeably; he became apathetic and seemed to lose his previous ambition and interest in things. He himself was fully aware of this change, and he complained in addition of some difficulty in thinking. About the middle of February, however, he succeeded in obtaining work; but his wife believes that it took him much longer at this time to tune a piano than it should have done. Early in March he visited relatives out of town because of the offer of outdoor employment away from the city and unconnected with his ordinary occupation. Though he seemed cheerful during this visit, wrote to his wife, and on the morning in question had bought a book which he was reading with interest, he took without warning an opportunity to commit suicide by inhaling illuminating gas, March 12, 1925, eight and one-half months after completing treatment. Afterward were found notes which he had postdated and concealed about the house, their content being of a markedly self-accusatory character. It is of interest that three months and also six months after the completion of malaria treatment the spinal fluid had become almost negative except for the colloidal gold curve.

Both this case and case 4, it should be noted, might have been, and in fact were, at one time, regarded as complete remissions; only the subsequent turn of events, one year and a quarter and six months respectively, after treatment, made it necessary to regard the outcome as less satisfactory.

Among these thirteen cases of incomplete remissions we have five examples in which at one time was attained a greater degree of clinical improvement than was subsequently maintained; and since this is a characteristic of scarcely any of the cases to be considered under the next heading, it may be stated here in summary that of the preceding fifty-six patients who survived the malaria treatment, a total of twelve have exhibited an unquestionable subsequent modification in the therapeutic result earlier achieved. The occurrence of cases of this sort raises the question whether one may apply to the malaria treatment the supposition that has been indulged in with regard to foreign protein therapy in general, as "a method of stimulation whereby all the forces of cellular and humoral resistance are for a short period of time keyed to the highest pitch."[18] But in the case of the malaria treatment of

18. Petersen, W. F.: Protein Therapy and Nonspecific Resistance, New York, the Macmillan Company, 1922, p. 247.

general paralysis, before we can commit ourselves to a view of this sort (save on other as yet undiscovered grounds), we must know whether these twelve cases are the exceptions or the rule; in other words, whether these are simply the cases in which the dying out of this "activation" comes about earliest, so that it is only a question of the further lapse of time before the "arrested" unimproved cases, and also eventually even the full remissions, make the downward turn; or whether, on the other hand, those few cases in which no "activation" takes place or in which it is a relatively evanescent phenomenon are to be distinguished altogether from the others, in which the alterative impetus furnished by the treatment leaves them more or less permanently well above, even if in varying degrees, the *status quo ante*.

FULL REMISSIONS

In this group are included those patients who are enabled to leave the hospital and return to their former occupations. Since "Arbeitsfähigkeit," however, is not, for obvious reasons, an altogether equitable criterion, we may add that these patients are characterized by a minimal degree of defect symptoms in the intellectual sphere and by more or less complete insight into the fact and nature of the previous mental disorder. This, however, is not to say that these patients are free from other evidence that they had been the victims of outspoken general paralysis. On the contrary, there are to be found in many of them more or less subtle indications, especially in the emotional realm, of some alternation, often quite unimportant, in the personality. One patient, for example, exhibiting now for well over a year a remission astonishingly complete in all other respects, is said by his wife to laugh rather more readily, and also rather more loudly, than had formerly been his wont—a difference not very marked and purely of degree. Another patient, an unusually intelligent and able man, said, "I am not quite the man I was; things require more effort than they did; I haven't got the 'wallop' I had three years ago"; he is aware of a reduction in his former initiative and self-confidence, such that he shrank from undertaking business projects regarding which he would formerly have felt no hesitation whatever.

A final characteristic of this group may be mentioned: they have exhibited, at any rate as yet, a tendency almost without exception to maintain the degree of mental improvement which they have achieved; the only exceptions to this statement so far observed have been the two patients, in cases 4 and 5, and perhaps in case 2, and a recently treated patient of the "manic" type, somewhat comparable to the one in case 5, who four months after achieving a very complete remission, developed a severe depression now of two months' duration. Yet in

the nature of things, striking though the present situation in this respect appears to be, such an opinion must be tentative as we have already hinted, and must remain so for another five years at least, since nothing less than the question of the permanence of these remissions is here involved. At present our impression is based on thirty-seven cases, in only five of which full remissions have been manifested for less than six months, the remainder having continued in this state for periods of from nine months to two and one-half years.

Regarding the persistence of physical signs, we have yet to encounter a patient in whom we have been convinced of a definite modification in the reaction of the pupils or in the tendon reflexes. On the other hand, we have observed occasional instances of considerable improvement in ataxia, and of some not conspicuous improvement in facial tremor and in speech defect.

It is inevitable, in sum, that the patients in this group should present certain differences among themselves with regard to the persistence of residual manifestations in the mental sphere, and yet be classifiable among the full remissions. What is more remarkable is that within this single group should be found patients in whom the duration of objective evidence of the disease prior to treatment should be so widely variable—indeed, in not a few instances greater than in some patients whose mental outcome has been much less successful. We will cite three patients in whom the therapeutic result, although no more gratifying in itself than that in a number of others and perhaps somewhat less so, has been distinctly striking in view of the long delay which had occurred before they received treatment.

REPORT OF CASES

CASE 6.—H. T. M., a lawyer, aged 55, admitted Nov. 23, 1923, had begun two years prior to admission to look "run down," to suffer from frequent nausea and vomiting, and to be rather "nervous" and irritable. About six months before he was admitted he began to be distinctly forgetful, to require an abnormal amount of sleep, and to be easily fatigued. Within a month he developed dulness of comprehension and slowness in his grasp of and response to things said to him; his behavior became distinctly erratic in minor ways. He shortly became hyperactive, voluble and expansive; exhibited markedly defective judgment and lost all sense of responsibility. For about two months prior to admission there was a temporary lull in these manifestations; but shortly after admission he began to retrogress definitely, lost weight rapidly, and became distinctly depressed; a marked hypochondriacal trend was conspicuously present. Four months after admission, March 11, 1924, he made a sudden impulsive suicidal attempt, running the length of the corridor to batter his head against the wall. While there was no evidence of a fracture of the skull, he remained for a week in a state of partial stupor, much confused, amnesic for the accident, disoriented and with a marked speech defect. By March 31 he had reached a weight 26 pounds (12 Kg.) below his admission level of 191 pounds (87 Kg.).

One month after the attempt at suicide he was inoculated with malaria (April 12), completing the course of malaria April 30 (eight paroxysms). Almost immediately from the latter date he began to evince definite improvement. In exactly six weeks he gained 32 pounds (14.5 Kg.), showed distinct improvement in his memory for recent events and exhibited a perfect degree of insight into his condition at the time of the suicidal attempt and during the year previous. In fact, it was possible to discharge him from the hospital eight weeks after the completion of the malaria treatment, June 6, 1924. It required the greater part of the ensuing year, however, for the degree of improvement now present to come about, for it took the larger part of this period for the gradual but progressive change to take place whereby the patient became less prone to be upset by noise or confusion of any kind, to take the wrong direction in the street and to misidentify the doors in his house, for example, and in general to exhibit a somewhat impaired grasp of his environment. Even when these appearances were most marked and seemed most definitely pathologic, they represented, rather, a certain not very excessive exaggeration of normal traits, among them a considerable tendency to absent-mindedness and "woolgathering," a poorly developed sense of direction, a generally somewhat defective contact with the immediate environment, and a hypochondriacal type of reaction. His insight into the finer details of these residuals was not altogether complete; at the same time he was fully aware, even to the point of exaggeration, of his gradual return to what he considered his normal level of mental and physical efficiency. He has recently obtained a responsible and well paid position with a law firm; but how successfully he will be able to perform his duties remains to be seen.

Throughout the past six months his weight has been stationary, at a level 10 pounds (4.5 Kg.) below the maximum which he had achieved nearly a year earlier. Although some 18 pounds (8 Kg.) above his weight at the time of malarial inoculation, his present weight is essentially the same as his weight on admission to the hospital.

It is of interest that this patient's spinal fluid became practically negative at the end of one year from the completion of malaria treatment (on April 30, 1925), and has remained so since. The Wassermann reaction is + in 0.8 cc. of fluid with a cholesterinized antigen only; the colloidal gold curve is practically normal. The blood Wassermann reaction is + + with a cholesterinized antigen (Dec. 1, 1925). This patient received no specific treatment either before or after his course of malaria, except for eight injections of tryparsamide (3.0 Gm. each) some three months before his malarial inoculation.

We would add that in eight patients in the present series an essentially negative condition of the spinal fluid has come about, without the use of treatment other than malaria, at an interval after the completion of treatment of from nine months to a year and one-half.[7]

Case 7.—D. V. S., a chauffeur, aged 45, admitted March 30, 1924, had first presented certain somatic complaints somewhat more than four years previously and then within a few months had begun to manifest a certain "let-down" in the form of evading responsibilities, of shifting decisions to his wife. Nearly three years prior to admission he had exhibited a marked tendency to sleep, and within three months he had become distinctly forgetful and also more quiet and reserved than usual. During the next two years and a half he became progressively more inefficient in his work, although he was able to obtain employment at

intervals until within three months of his commitment. On admission he was extremely dull and apathetic, was irritable and negativistic at times, manifested a marked retention defect, and exhibited an apparently gross degree of mental deterioration; insight was completely lacking.

He was inoculated with malarial blood, April 29, 1924, and underwent twelve febrile paroxysms between May 6 and 18. Within three weeks of the latter date he was showing definite improvement with regard to emotional stability, obstinacy and uncooperativeness, and also with respect to his contact with the surroundings, not only no longer becoming confused as to locations about the ward but also losing much of his former apathy. At the end of three months from the completion of treatment he weighed 14 pounds (6 Kg.) more than he had immediately prior to treatment. At the end of six months he had gained so greatly in alertness that he was able to act as messenger for the ward. At the end of nine months, Feb. 25, 1925, his gross retention defect had become inconspicuous and he no longer exhibited evidence of personality deterioration; but his insight was partial only. At the end of thirteen months from the final malarial paroxysm he was discharged, June 23, 1925, having by this time acquired an acceptable degree of insight, and improved greatly in his reproduction of school knowledge and somewhat in his calculating ability; he showed practically no vestige of memory or retention defect, and there was no deterioration of the personality and no indication of judgment defect. His speech remained deliberate but without actual dysarthria, although at times some circumoral tremor was apparent. The pupils had never been abnormal save to a minimal extent. His weight was some 10 pounds (4.5 Kg.) above his pretreatment weight. The Wassermann reaction in the spinal fluid had become negative in 0.15 cc. (both antigens), but was still + + + + in 0.4 cc. The colloidal gold curve had undergone a slight modification to 4443211000. The Wassermann reaction in the blood was ± with an alcoholic antigen; + + + + with a cholesterinized antigen. These were the findings on Aug. 20, and Nov. 17, 1925.

The patient has not resumed his former occupation as a chauffeur, but has worked continuously since his discharge as helper in a restaurant. There has been no reason to modify the impression which he made at the time of his discharge six months ago.

Case 8.—H. A. L., an insurance clerk, aged 40, admitted April 29, 1924, nearly two years before had manifested undue fatigability and a considerably increased tendency to sleep, while a definite and wholly uncharacteristic irritability made itself evident more than a year and a quarter prior to admission. A year later, in January, 1925, much more unequivocal mental symptoms began to assert themselves, and three months later his conduct became obviously irrational, with an accompaniment of marked elation, volubility and grandiose ideas, a number of which he translated into action. In spite of his irrationality he managed somehow, however, to continue at his occupation until the very day of his removal to the observation pavilion. Unlike the patients in cases 6 and 7, this man received a small amount of antisyphilitic treatment prior to admission, consisting of twelve injections of neo-arsphenamine in the latter part of 1917 (immediately after the appearance of the primary lesion), and ten injections of the same drug in the spring of 1923.

On admission the patient was extremely restless and talkative. He manifested a marked degree of absorption in his grandiose ideas, which appeared to attain the vividness of hallucinations, auditory as well as visual; there was a religious coloring to many of his delusions. He was extremely euphoric and somewhat

boastful, occasionally irritable or angry; there were also brief periods of apparent depression. On seven occasions it was necessary to catheterize him, since he paid no attention to the need for emptying the bladder.

He was inoculated with malarial blood on May 17, 1924, and underwent eleven febrile attacks between May 24 and June 6.

Two weeks later he began to show a gradual but consistently progressive reduction in his psychotic manifestations; during the succeeding three weeks (June 13 to July 4) he gained 23 pounds (10 Kg.). At the end of this brief period of five weeks, indeed, mental recovery appeared to be essentially complete. This was notably true in regard to insight, while he was able to give a particularly detailed account of the content of his delusions. He felt certain that the transition from a state of mental abnormality to one of relative normality was a very abrupt one which he could place within an hour! It is hardly to be expected that these patients, however rapid or complete their mental improvement, will retain a detailed memory of the actual period of the psychosis, especially its acute phases. This patient, however, could recall more than the ordinary in this respect, although he had complete amnesia for the period from April 14 to 22, shortly before admission, and for the latter part of his stay in the observation pavilion. By the end of July only a mild and doubtfully pathologic euphoria remained, and it was possible to discharge the patient Sept. 4, 1924.

His company, however, refused to take him again into active employ, but on the other hand, kept him on the inactive list on full pay. This was a severe disappointment to the patient, as it also precluded his taking up another occupation; at the end of a year the patient, put on half pay and free to do other work, obtained a position as hotel clerk. During the same interval he also had various domestic difficulties to contend with, but to these—and we think this is of some importance—he has made as excellent an adjustment as he did to the severe disappointment of not returning to his former position.

The preservation of the personality is in this patient, too, a conspicuous feature. At the same time he is inclined to a mild degree of forgetfulness, and it is stated that he has a tendency to occasional irritability such as was not a part of his normal make-up.

The spinal fluid picture has been atypical in one respect. Almost always we have observed a prompt reduction of the cell count to normal immediately on the termination of the febrile period; we have come to regard with suspicion those few patients in whom this does not occur or in whom there soon takes place an elevation of the cell count subsequent to a more or less normal condition in this respect. In this patient the cell count was 4 on June 17, 1924, immediately after the final attack of malaria, the pretreatment pleocytes having varied from 19 to 50 on three occasions. On July 7, however, the lymphocytes had risen to 19 per cubic millimeter, and on September 2 to 27; on October 7 the cell count was reported as 117. There was, nevertheless, no change whatever in the patient's mental condition. A course of tryparsamide was then begun. One week after the first injection the cells numbered 36 per cubic millimeter; after twelve injections the cell count was normal and has since remained so. On the other hand, the Wassermann reaction has remained practically as strongly positive (++++ in 0.15 cc. to both antigens) after a total of thirty-six injections of tryparsamide (3.0 Gm. each) and twelve injections of neo-arsphenamine (0.6 Gm. each) as it was before this additional treatment was begun. The colloidal gold curve has been nearly normal for the past six months. The Wassermann reaction with the blood remains ++++ with both antigens.

Apart from the excellent remissions they achieved and the conspicuously complete degree of preservation of the personality that characterized them, these three patients had in common a positively ascertained considerable duration of the mental disease before they came under treatment, such that they might have seemed not altogether satisfactory cases from which to expect a favorable response to therapy. Yet even residual defects were almost minimal in these three patients; indeed in case 7, that of the man who had by far the longest duration, which was, moreover, of the simple dementing type of general paralysis, exhibited such residuals perhaps least of all. In our opinion the malaria treatment would deserve fully the favorable report made of it if it accomplished only once in fifty times such results as were obtained in these three cases. Yet we would not imply that these three patients represent the high-water mark of therapeutic success with this form of treatment, for there are a number of other cases among this group of thirty-seven in which, from the standpoint of duration of the mental disorder, of the clinical type of general paralysis present, of the complete freedom from residual defect symptoms achieved and of the duration (now more than two years in twelve of the thirty-seven) of the remission so far attained, the therapeutic outcome has been equally gratifying.

CONCLUSIONS

As to the clinical types, so called, represented by this series of patients, for this appears to be one of the most definite points bearing on the prognosis, we have to recognize that the division into types is somewhat arbitary and artificial, it being often particularly difficult to mark off a definite boundary between the expansive patients, whose expansiveness is frequently accompanied by some definite degree of motor restlessness, and the hypomanic "agitierte" patients whose motor unrest is an even more prominent feature than the expansiveness which always accompanies it. In terms of this somewhat loose classification, then, we find that of the 106 patients, fifty-six, or 53 per cent, were of the simple dementing type; twenty, or 19 per cent, of the expansive type; eighteen, or 17 per cent, of the "manic" type; in six ideas of persecution dominated the clinical syndrome, and two presented a catatonic picture. Results with reference to the therapeutic outcome are presented in table 2.

It is thus evident that whereas cases of the simple dementing type make up 53 per cent of the entire series, they number only 19 per cent of the full remissions, while 62 per cent of the full remissions are of either the expansive or the "manic" type of general paralysis. Expressed in another way, only 12 per cent of the cases of the simple dementing type achieved full remissions, whereas 55 per cent of the expansive type,

and 67 per cent of the "manic" type, attained a maximum therapeutic result. On the other hand, 14 per cent of the simple dementing cases achieved moderate remissions;[19] and since the difference between the moderate and the full remissions largely depends, it is very possible, on factors which have nothing to do with the treatment per se, it may be pertinent to call attention to the fact that 27 per cent of the cases of the simple dementing type achieved remissions of one grade or the other, as compared with the 65 per cent of the expansive type and the 83 per cent of the "manic" type to which the same statement applies. Conversely, 61 per cent of the simple dementing group remained unimproved, grew worse or died; whereas this could be said of only 30 per cent of the expansive, and of only 17 per cent of the "manic" cases.[20]

TABLE 2.—*Therapeutic Outcome in One Hundred and Six Cases*

	Simple Dementing	Expansive	Manic	Paranoid	Catatonic	Unclassified	Total
Full remissions	7	11	12	2	1	4*	37
Moderate remissions	8	2	3	0	0	0	13
Slightly improved	7	1	0	0	0	0	8
Unimproved	18	4	1	3	0	0	26
Died	16	2	2	1	1	0	22
Total	56	20	18	6	2	4	106

* These four patients were seen very early, while still in the "neurasthenic" stage. Since they were only very mildly psychotic as compared with all the other patients in the series, it is perhaps fairest to leave them unclassified as to type.

We may epitomize our present experience of the varieties of possible response to the malaria treatment as follows: (*a*) a progressive downward course practically from the completion of treatment (two cases); (*b*) an essentially stationary course for three months or longer, then decline and death (six cases); (*c*) a stationary course of indefinite duration—observation period from four months to two and one-half years (twenty-five cases); (*d*) a slight but definite mental improvement, eventually followed by decline (five cases); (*e*) a considerable improvement with eventual decline of various degrees (four cases); (*f*) a marked improvement with eventual decline of various degrees (four cases); (*g*) slight improvement, thus far maintained—observation period from six to fourteen months (five cases); (*h*) moderate remis-

19. It is well to remember that, in general, the patients of the simple dementing type are brought for treatment considerably later than the expansive and especially the "manic" patients.

20. If the thirteen patients who died during or shortly after the course of malaria are singled out, it is found that twelve of these were of the simple dementing type. This preponderance appears too great to be atttributable to coincidence; perhaps a partial explanation is to be found in the fact already mentioned that patients of this type come much later, in general, for treatment.

sions, thus far maintained—observation period from four months to one and one-half years (eight cases) ; (*i*) full remissions, thus far maintained —observation period from five months to two and one-half years (thirty-six cases).

What we do not know, and what it is important to know, is whether such a subdivision as the foregoing has anything but a provisional value; whether those patients whose moderate improvement or even apparent "recovery" has been maintained for many months will sooner or later join the group, as yet greatly in the minority, who fell from the maximum level previously attained—so that the ultimate outcome will prove to be the same in the entire group of malaria-treated general paralytic patients, differing only in the length of time elapsing before eventual retrogression comes about. Little as such a possibility may seem at present to be suggested by the behavior of the full remissions in particular, or by the more extended experience of the Vienna clinic,[21] the question is one on which only time can throw full light.

SUMMARY

1. Between June 1, 1923, and March 15, 1926, 116 male patients, in nearly all cases patients with general paralysis, have been inoculated with tertian malaria, representing fifty-four successive passages from host to host, since Sept. 15, 1923, of the same strain of *Plasmodium malariae*. Of these, 106 cases of undoubted general paralysis are here considered.

2. Of the 106 patients twenty-two have died, thirteen during or shortly after the course of malaria (in eleven of these the malaria was directly responsible for or did something to hasten the fatal termination), and the remaining nine at intervals of from two to eleven months after completing treatment; twenty-six are classed as unimproved; eight are classed as slightly improved; thirteen have attained moderate remissions, and thirty-seven we regard as having achieved full remissions. Among the latter, the duration of the full remission has been more than a year in twenty-one cases, and more than two years in twelve cases; in only five cases is it now less than six months.

3. Of the cases of the simple dementing type, 12 per cent achieved full remissions and 14 per cent moderate remissions; of the expansive cases this was true of 55 per cent and 10 per cent, respectively; of the "manic" cases, of 67 per cent and 16 per cent, respectively.

21. Gerstmann (footnote 9, pp. 200-210). The writer holds that remissions brought about by malaria treatment differ from spontaneous remissions in the essential respect that the former, in his experience, are ordinarily of much greater duration. He quotes Nonne to a similar effect.

4. We are inclined to believe that failure of the treatment depends on the presence of one or both of two factors: anatomic changes beyond the possibility of functional restitution; inability of the organism to react to the treatment with certain indefinable alterations (Umstimmung) of which there exist hints in certain phenomena which have been observed in connection with foreign protein therapy in general. This view of the situation is admittedly hypothetic, and is put forward to call attention to the need for further investigation of the mechanism of the malarial treatment of general paralysis.

MALARIA INOCULATION IN THE TREATMENT OF GENERAL PARALYSIS

RESULTS IN FORTY-TWO CASES *

HOWARD D. McINTYRE, M.D.
AND
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CINCINNATI

The observation that some patients with general paralysis improve after an intercurrent febrile attack is almost as old as the knowledge of the disease. In a paper dealing with this fact Wagner von Jauregg, as early as 1887, advocated the treatment of general paralysis with malaria. In 1909 he used tuberculin combined with mercury as a means of inducing fever in the treatment of general paralysis. A few general paralytic patients treated by this method were still in remission in 1921. Following his experiments with tuberculin, he used typhus vaccine as a fever producing agent with fairly good results. In 1917 he inoculated nine general paralytic patients with benign tertian malaria. Of this group three were reported still in remission in 1922.[1]

Since Wagner von Jauregg's pioneer experiments, many methods of inducing fever in the treatment of general paralysis have been tried: E. Meyer [2] rubbed Autenrieth's ointment on the scalp in order to induce suppuration; Böhmig [3] used milk injection with indifferent results; Fischer [4] of Prague reported 50 per cent remissions after injections of sodium nucleinate; Plaut and Steiner advocated the use of relapsing fever; Sagel [5] used African relapsing fever in seventy-two cases with good results and reported no deaths resulting directly from the treatment.

In connection with the malarial treatment of general paralysis, the report of Delgado [6] of Lima is of interest. He states that in Peru a leishmaniasis of the skin and mucous membranes, known by the natives as "uta," is very prevalent. At certain seasons of the year sufferers from "uta" make pilgrimages to a district known as Tembladera in which malaria abounds. The pilgrims become infected with malaria and

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* Read before the Daniel Drake Society (Cincinnati Research Society) Jan. 8, 1926.

1. Wagner von Jauregg: J. Nerv. & Ment. Dis. **55**:369 (May) 1922.
2. Meyer, E.: Berl. klin. Wchnschr., 1877.
3. Böhmig, W.: Arch. f. Psychiat. **5**:71 (Sept.) 1924.
4. Fischer, O.: Med. Klin. **17**:1509 (Dec. 11) 1921.
5. Sagel: München. med. Wchnschr. **71**:369 (March 21) 1924.
6. Delgado: J. Nerv. & Ment. Dis. **55**:376 (May) 1922.

are cured of the "uta." Bercovitz,[7] writing from Hainan, China, states that 90 per cent of the population of three millions is infected with malaria; syphilis is practically universal, and yet in eight years he has seen no cases of general paralysis and only two or three cases of tabes. De Bellard[8] sees 1,000 patients a month, 50 per cent of whom have syphilis, yet he has never encountered a case of general paralysis.

Since 1919, Wagner von Jauregg has treated more than 200 cases of general paralysis with over 30 per cent complete remissions. According to the best statistics obtainable, spontaneous remissions occur in only about 3 per cent of untreated general paralytic persons. Gerstmann[9] reports 38 per cent remissions in 278 cases treated with malaria; Lewis, Hubbard and Dyer[10] report sixteen remissions in fifty takes; Askgaard had 32.4 per cent complete remissions, and 21.6 per cent partial remissions.

TECHNIC

Wagner von Jauregg's technic is as follows: from 1 to 4 cc. of benign tertian malarial blood is injected subcutaneously or intramuscularly. The patient is allowed to have eight or nine chills, occasionally ten or twelve. Quinine bisulphate is then given in doses of 7½ grains twice daily for three days; then 7½ grains (0.5 Gm.) is given once daily for fourteen days. Following the quinine treatment, six injections of neo-arsphenamine are given, beginning with 0.3 Gm. and increasing to 0.6 Gm., one week apart.

Our technic is slightly different. We inject 6 cc. of benign tertian malarial blood into the gluteal muscles, and allow from eight to sixteen chills depending on the physical condition and reaction of the patient. Following the chills, bisulphate of quinine, 1.0 Gm., is given twice daily for ten days. This is followed by Fowler's solution in doses of 3 minims (0.2 cc.) three times a day, increasing by 1 minim per dose daily until the patient is taking 10 minims (0.6 cc.) three times a day. This dose is continued for thirty days. Fowler's solution was used to avoid complicating the serologic results by the effects of neo-arsphenamine.

RESULTS OF INOCULATIONS

From Sept. 10, 1924, to March 18, 1925, we inoculated forty-two general paralytic patients with benign double tertian malaria certified by the medical department of the University of Cincinnati, and secured through the services of Dr. H. B. Weiss of the Department of Medicine

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7. Bercovitz, Nathaniel: Neurosyphilis and Malaria, J. A. M. A. **82**:1713 (May 24) 1924.

8. De Bellard: Gac. méd. de Carácas **32**:193, 1925.

9. Gerstmann: Ztschr. f. d. ges. Neurol. u. Psychiat. **81**, 1923.

10. Lewis, N. D. C.; Hubbard, L. D., and Dyar, E. G.: Am. J. Psychiat. **4**: 175 (Oct.) 1924.

and Dr. Harry Claassen of the Department of Dermatology. Of the forty-two patients inoculated, two failed to "take" even on repeated inoculation. In this connection Jauregg states that some persons are immune to inoculation malaria.

Of the forty remaining patients, nine died during the course of treatment or within one month following it. These fatalities will be discussed in considering the complications.

Three patients died in from six months to one year following the treatment. These deaths have no possible relation to the treatment.

Eight patients are in a complete remission at present, fifteen months after the first inoculation. By complete remission it is meant that they have recovered physically and mentally to a point at which their original earning power has been restored.

Four patients have had remissions to the extent that they are living outside the hospital and are earning a living. An enthusiast might consider these patients as in complete remission, but the results have not been as good in them as in the first eight patients. One patient is still in the hospital. He would be able to earn his living on a simple scale and we have included him in the second group.

Six patients have improved to a point at which they are good hospital helpers under supervision. Two patients have shown great relative improvement, having changed from a state of practical amentia to one in which they are oriented for time and place; there has been some restoration of memory and they are able to care for their persons.

Seven patients have shown no improvement.

The results may be tabulated as follows:

Complete remissions	20 per cent
Almost complete remissions	12.5 per cent
Improved	20 per cent
Unimproved	17.5 per cent
Dead	30 per cent

EXAMINATION OF PATIENTS

Previous to inoculation all patients were subjected to complete physical, psychiatric, and laboratory examinations, including: blood Wassermann tests, blood count, and estimation of blood urea nitrogen, carbon dioxide combining power of blood plasma and blood sugar; the spinal fluid was examined for the Wassermann reaction, Lange's colloidal gold curve, globulin test, and cell count; a chemical and microscopic examination was made of the urine. The patients selected were in good physical condition, except in a few instances when the patient's guardian insisted that the patient be given a chance of benefit by treatment in spite of poor physical condition. All patients showed the clinical signs of general paralysis.

During treatment the blood was examined for parasites, and blood counts and chemical analyses were made as often as was indicated. A quantitative blood Wassermann test, using from 0.01 to 0.1 cc. of serum in ten tubes, was made before, during and after treatment. No marked serologic changes in the blood or spinal fluid were observed that can be

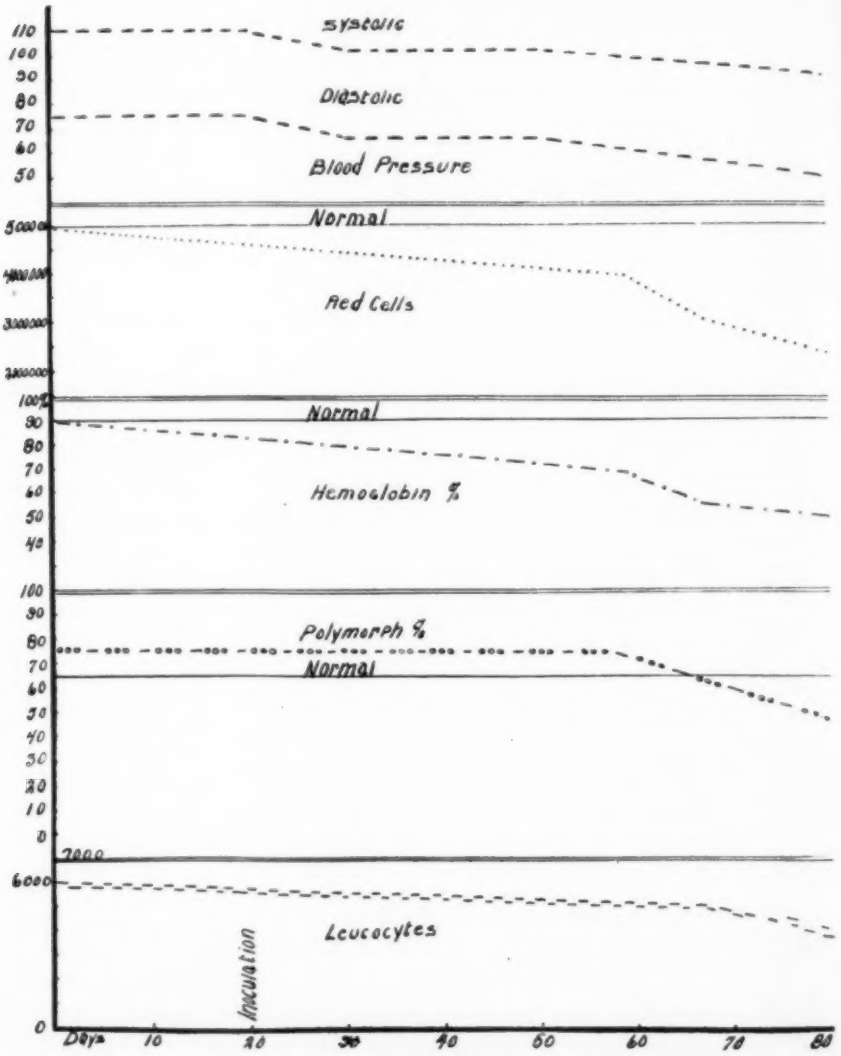

Chart 1.—Blood pressure, erythrocytes, hemoglobin and leukocytes in case 1.

correlated with the prognosis or with the therapeutic outcome. The blood Wassermann reaction may become negative to the most sensitive modifications of the test in a case showing no improvement clinically; and, on the other hand, a strongly positive blood Wassermann reaction

may persist throughout the course of a case which shows marked clinical improvement. The most striking observation made in the serology was: in three cases the blood Wassermann reaction became negative during the course of the malarial fever before quinine or arsenic had been given.

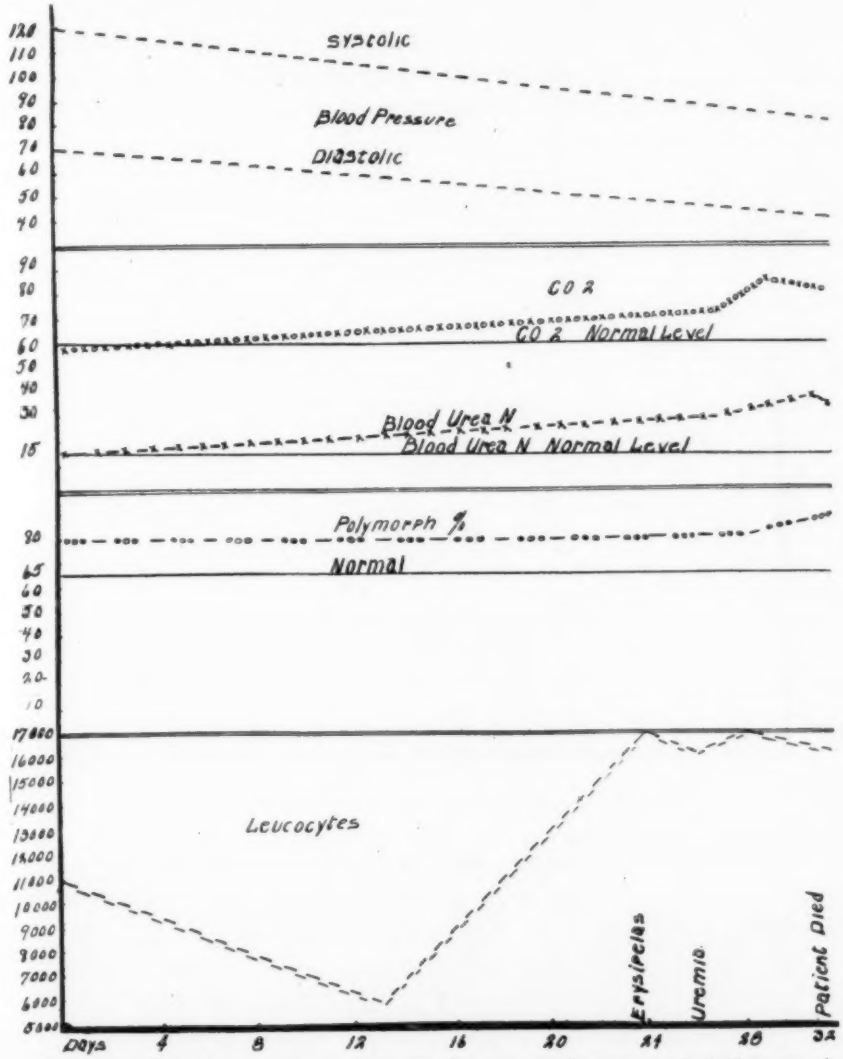

Chart 2.—Blood pressure, carbon dioxide, urea nitrogen and leukocytes in case 2.

The most valuable results of laboratory examinations observed for prognosis, especially as regards complications, are: estimation of the blood urea nitrogen, and the blood count. In an uncomplicated case of malaria, the blood showed secondary anemia, and leukopenia with

relative lymphocytosis (chart 1). This blood picture was considered reasonably safe. When polymorphonuclear leukocytosis developed it indicated that the patient was developing some complication (chart 2).

COMPLICATIONS

1. *Pyogenic Infections.*—Malaria in some instances lights up quiescent pyogenic foci. In our series were three cases of peritonsillar abscess, two of parotitis, one of erysipelas and one of abscess of the calf of the leg from which a quart of staphylococcus pus was drained at one incision.

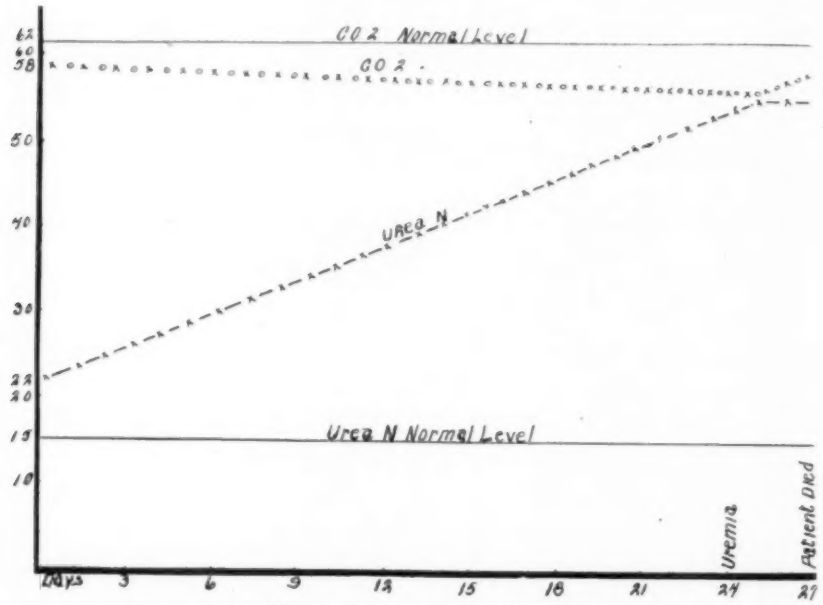

Chart 3.—Carbon dioxide and urea nitrogen in case 3.

2. *Uremia.*—Two patients developed uremia during the course of the treatment. In one, the malaria had proceeded for four days when erysipelas developed. The malaria was terminated by the administration of quinine hydrochloride intramuscularly. Acute nephritis developed and was followed by uremia. The patient was brought out of coma on two occasions by the administration of 4 per cent magnesium sulphate solution intravenously but finally lapsed into coma and died (chart 2). The other case of uremia developed during the course of the malaria. The malaria was terminated but the patient died in uremic coma (chart 3). The urea nitrogen content of the blood is an excellent indicator of impending uremia in such cases. It will be noted that the patient to whom chart 3 refers had a urea nitrogen content at the

pathologic level at the beginning of treatment; perhaps he should not have been inoculated.

Circulatory Collapse.—Three patients collapsed into a condition resembling shock, with rapid thin pulse, sighing respiration and cyanosis. Two recovered with stimulation, but one died.

Acute Bulbar Palsy.—Three patients died with symptoms of acute bulbar palsy.

Convulsions.—One patient died in a paretic convulsion during the course of the malaria. This convulsion occurred in the afebrile stage.

Analysis of Fatalities.—One patient committed suicide in the acute hallucinatory confusion which usually accompanies the fever. Three patients developed acute bulbar palsy during the course of the chills. One patient dropped dead suddenly two months after treatment had been completed. This death was in no way related to malaria. One patient died of circulatory collapse during the chills. One patient developed erysipelas, acute nephritis, and uremia; he died after the termination of the malaria; the malaria in this case had lighted up a quiescent infection. One patient developed uremia and died after the malaria had been terminated.

COMMENTS

Facts Concerning Inoculation Malaria.—Inoculation may be made at any time during the course of the malaria and does not have to be made during or after a chill.

A strain may be passed from patient to patient indefinitely. Wagner von Jauregg passed one strain through thirty-seven generations.

Some patients are immune to inoculation malaria.

Attacks may vary from tertian to quotidian type.

Inoculation malaria is very sensitive to quinine.

Physical and mental improvement in malarial treated general paralytic persons go hand in hand.

In all possibility inoculation malaria becomes entirely asexual in type and cannot be transmitted by the mosquito.

Death Rate.—Reese and Peter [11] report a death rate of 10 per cent; MacBride and Templeton [12] report three deaths in eighteen cases; Lewis, Hubbard and Dyar report thirteen deaths in fifty-one cases.

In our series we believe that the malaria was directly responsible for the deaths of four patients. This would make the death rate 10 per cent. Five deaths were in no way related to malaria. In the remaining deaths the end was probably hastened by the malaria.

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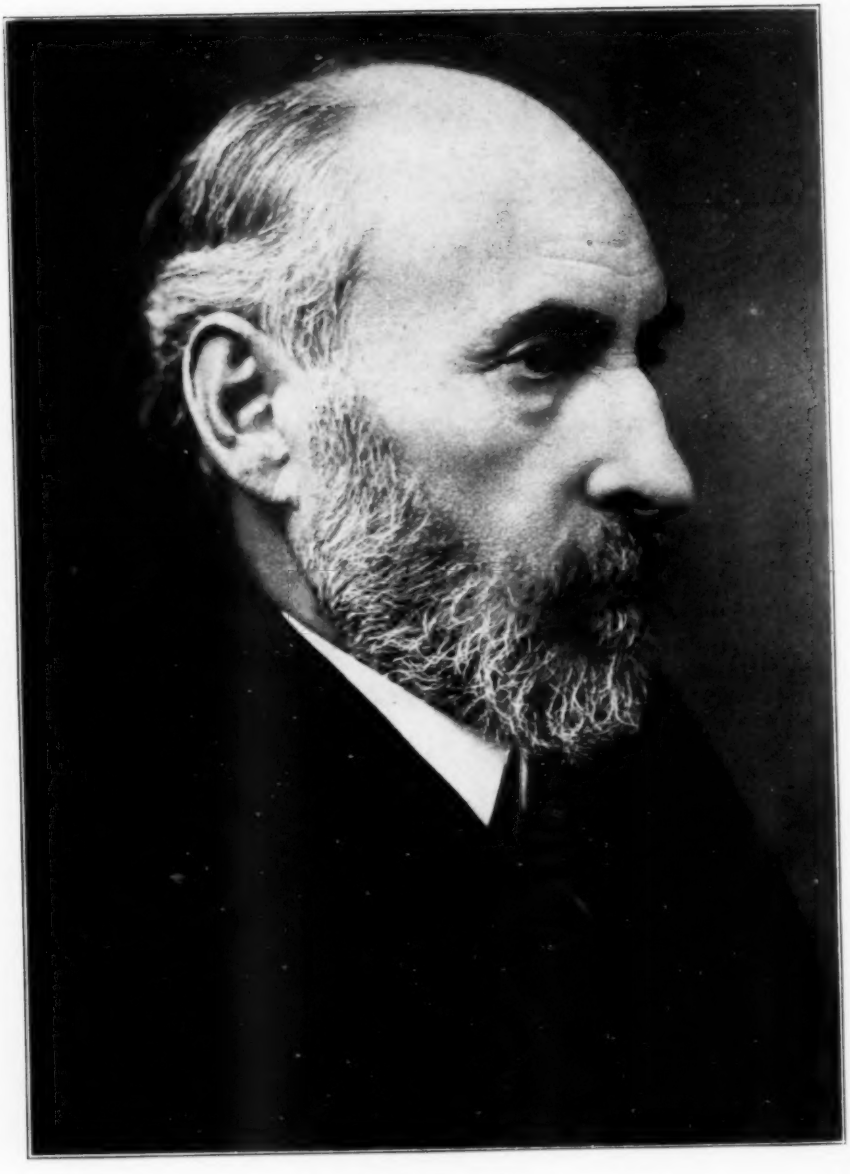
11. Reese, H., and Peter, K.: Med. Klin. **20**:372 (March 23) 1924.

12. MacBride, H. J., and Templeton, W. L.: J. Neurol. & Psychopath. **5**:13 (May) 1924.

Contraindications for Malaria Treatment.—(1) Run down general physical condition with circulatory asthenia—in such cases the patients should be built up with arsenic before treatment is begun; (2) anemia; (3) kidney lesions as evidenced by blood urea nitrogen and urine examination; (4) heart lesions with myocardial degeneration; (5) patients with a consistent leukocytosis should be thoroughly examined for focal infection and put in good general health before inoculation; (6) patients in cases that belong to the meningovascular type of cerebrospinal syphilis with localized lesions are poor risks because the malaria exaggerates these conditions; malaria itself tends to produce thrombosis and hemorrhage in the vessels of the central nervous system.

CONCLUSIONS

The malarial treatment of general paralysis is a distinct advance in the treatment of this disease, but it is not without danger. It is essentially a form of treatment for hospital application. It requires wide knowledge of internal medicine and should be carefully controlled from both the clinical and the laboratory standpoint if the percentage of fatalities is to be kept at a minimum.



DON SANTIAGO RAMÓN Y CAJAL

SPECIAL ARTICLE

THE CAREER OF RAMÓN Y CAJAL

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NEW YORK

> It has been said many a time that the problem of Spain is a problem of culture. It is necessary in fact, if we would enroll ourselves with the civilized peoples, that we cultivate intensively the deserts of our land and brain thus rescuing by prosperity and mental vigor all those national riches that have been lost in the sea and all those talents which have been lost in ignorance.

These words were scrawled in Spanish across the portrait of Ramón y Cajal. I had been conscious of keen eyes looking down from out that portrait during my first day of work in the laboratory of Pio del Rio-Hortega, and finally stopped to decipher the scrawl. Before coming to Spain I had learned much of the scientist Cajal, the great master of the Spanish school of neurology, from his scientific publications. But the writer of these words must be more than a closeted scientist; a critic, a prophet perhaps, certainly a master of literary style.

In America it had been rather difficult to explain how one could profitably spend six months in Spain learning new methods of medical research. But here in Madrid, Cajal, the winner of the Nobel prize, was a figure much talked about though rarely seen. His name seemed to be a password for had we not obtained entrance into a pension heretofore restricted to Spaniards by mentioning that I had come to work under the great scientist? In like manner did we not secure the little pisa for a permanent residence? The magic of his name made introductions easy and conversations immediately absorbing and satisfactory to the Spaniard, who welcomes above all else a tribute from abroad to the culture and intellectual distinction of his race.

In university and scientific circles Don Santiago, as he is called, seemed to be a sort of dean and censor; to educational reformers a much needed ally, and in politics a figure whose power is recognized even by the Dictator Primo Rivera. The peasant and the townsman understand nothing of his scientific work. It is enough for them that from foreign lands have come prizes and homage to this son of Spain, that he exhorts them to the stern virtues of their great ancestors and is himself a sign of the return of greatness to their land.

My first meeting with Cajal made a deep impression on me. It was in the library of his laboratory, and I found him sitting as though in

dejection, with head fallen forward on his chest so that only white hair and beard could be seen. His long arms hung down almost to the floor. As I hesitated in the doorway he started up and came forward with the graceful courtesy common to his race. With quick comprehension in his dark eyes he welcomed me as a foreign pilgrim to the laboratory and spoke of his great desire that the outside world should know of the achievements of the little group of scientists about him. Placing his hand on a shelf that held his own publications and those of his pupils, most of them in Spanish, he said with much feeling in his voice, "These books are unknown abroad. Scientists will not read Spanish. Almost every week I learn from German or American journals that men are rediscovering what I did long ago." With increasing agitation he expressed the fear that the Spanish school of neurology would be ignored and disappear after his death. Then with an abrupt change of manner he took my arm and added, "Let me show you the laboratory and I have here some photomicrographs in color which you will like to see." This first interview roused a desire to know more about the man—a desire easily satisfied, for his admirers were glad to talk, and there were his popular writings and autobiography.

Cajal, Spain's first great scientist, is a man whose genius may be compared with that of Pasteur. He comes, like Pasteur, from the people and developed spontaneously in his native land. When he was born in 1852, in the pueblo of Petilla, his father, Ramón y Cassasus, was practicing surgery among the poor peasants of the Pyrenees.

This pueblo, situated high on a treeless mountain, was connected with the outside world by a footpath only wide enough for man or donkey. The elder Ramón, who had caught from some long dead Aragonese ancestor a spark of restless ambition, had earned the degree of "Surgeon of the Second Class" under the most difficult circumstances. But not satisfied with that, he aspired to the more glorious distinction of a Diploma in Medicine, and, as a result of determined application to his mountain practice and the rigid economy of his household, he was able to come down from the Pyrenees, complete his medical education and finally bring his ever growing family to live in the university town of Zaragoza.

Thus the elder Ramón rose from his peasant home to a respectable professional position and a professorship in the university. He taught the boy Santiago to read French and, finding him quick to learn, determined that he should receive a medical education. Young Ramón, however, seemed to have inherited, in addition to his father's restless spirit, a talent for art. Doubtless this love of painting was quite natural, since he came from a race which has yielded so many great artists and lived in a country where interest in art is so prevalent.

His career in school was not brilliant. Too much of his time was spent in drawing and painting. An artist who came to decorate the church of the village in which the Ramóns were living at that time declared that the products of young Santiago's brush had no merit. However, some of his drawings done at the age of 8 have been preserved and it seems quite likely that members of the more realistic modern school of art would have found promise in them. At any rate, the artist's dictum confirmed his father's decision that the boy was to become a doctor of medicine, and away to the School of Catholic Fathers he was sent, to learn Latin. The schoolmasters found him indifferent and told him that he had no memory, a pronouncement he readily believed, like many another mistaught pupil.

The parent was puzzled, other schools were tried, and on two occasions he was removed from school altogether. At the first removal he was apprenticed to a barber, so that in case medicine failed, he should at least have a trade at which to earn an honest living. Perhaps the elder Ramón felt that as the barber is ancestor to the surgeon, the boy might somehow pass from hair cutting to surgery. The second time his school career was interrupted Santiago was apprenticed to a cobbler, for whose trade he showed so much aptitude that, at the end of a year, the cobbler desired him to sign for a long period.

There were other illicit schoolday enthusiasms in addition to art. One was an absorbing interest in the habits of birds, and another developed after he stumbled on a library of novels. Don Quixote and Robinson Crusoe seem to have been his favorites, and this admiration resulted in the writing of his first book, which was patterned after Crusoe's adventures.

Eventually, the despairing parent determined to take matters into his own hands. He himself undertook to teach the boy osteology, which he considered the cornerstone of medicine; and Cajal began dutifully to read about bones. But textbook pictures did not satisfy this student. He wanted to see these things for himself. And so he made a moonlit journey to the burying-ground, and braving the awful creatures of his imagination, he bore away the coveted models in terrified haste to an old granary. The granary became the classroom, and here father and son studied bones; and the boy at last found inclination and duty running parallel. The artist in him discovered an approved outlet, and he made pictures of bones large and small from every angle. Like Leonardo da Vinci he found a joy in drawing the component parts as great as that in reproducing the integrated living body; and like Leonardo he became a skilled anatomist.

When the family made their last move, to the capital of Aragon, the elder Ramón was appointed professor of anatomy in the University

of Zaragoza and the son was among his first pupils. The study of anatomy was continued for three years, and the new professor planned the publication of an atlas of anatomy based on his son's brilliant drawings. But this plan was never realized because of the impossibility of securing good reproductions.

Absorbing hobbies played an important part in Cajal's life from the start. During his university career he became the prey of a number of them. One of the most surprising was a mania for gymnastics. On discovering that an acquaintance had stronger wrists than he, he inquired and found that his adversary exercised habitually. Thereupon, young Cajal asserted that within six months he would excel this newfound rival. He immediately plunged into an intensive course of gymnastics to which he devoted two hours daily. After exhausting all the prescribed exercises he devised new ones, and not only vanquished his rival in less than six months but also became the champion strong man of the university gymnasium.

He observed later that the possession of such superlative strength made him long to exert it and humorously told the following tale. Among the university students at that time a certain young lady of the town was much celebrated for beauty of face and form. She was called "Venus de Milo" for no one had met her, and her true name was unknown. But of an evening she could be seen sitting on the balcony of her home, and Cajal often passed through that street in the hope of seeing her. One evening, when following his usual path homeward, he was accosted by another admirer who informed him that in the future he was to avoid this street. Cajal recognized the man as a student of the engineering school, a youth famed for physical prowess. Every muscle fiber in Cajal's sturdy body cried out for joy at the prospect of a struggle, and the two sought a secluded field of combat. First honors appear to have gone to the engineer, as he struck Cajal several mighty blows on the head with his stick, which made it impossible for him to wear a hat for days. At any rate the tide of battle turned and the young medical student encircled his opponent's chest in a mighty hug. Tightening his huge arms, he watched for the physiologic effect. There was not long to wait. The face of his adversary became livid, and he slipped unconscious to the ground. Horrified at the thought that he might have done him some irremediable harm Cajal revived his fallen rival, helped him to dress and assisted him to his lodgings. But it seems the beautiful "Venus de Milo" was not destined for either of them. She was carried off by envious microbes, a victim to tuberculosis.

In looking back at that period Cajal has remarked that his aptitude for intellectual work decreased rapidly. The brain, he says, fatigued

by its motor discharges apparently loses capacity for associative activity. The structural differentiation of the central nervous system seems to be suspended and activity of the higher centers superseded by that of the centers devoted to muscular control. This compensatory process, he feels, explains why the youths who excel physically are, with certain exceptions, not talkers and "possess a poor and rude intellect." However, he was prevented from becoming a victim of his athleticism by a severe attack of malaria acquired in Cuba. This, together with a subsequent almost fatal attack of pulmonary tuberculosis, relieved his cerebral gray matter of its burden of excess muscle.

Military service in Cuba followed the completion of his medical studies, and on returning to Spain he was appointed assistant in anatomy on the faculty of the University of Zaragoza. He then went to Madrid to be examined for his doctorate, and there for the first time he saw a microscope. His interest was immediately aroused, and he spent the savings that had accumulated during his long illness in Cuba to buy a microtome, a few books and a good German microscope, the first in the University of Zaragoza. From the books he learned how to make microscopic sections and began alone his study of the "infinitely small."

Several years later he won the contest for the professorship of anatomy at the university of Valencia and there, at the age of 32, he fitted up a little laboratory in his home and eked out his meager salary by coaching graduate students. There he began in earnest the work of investigation that has since added so much to our knowledge of the nervous system.

Scientific investigation was a thing quite foreign to the culture of Spaniards. They have always been a people passionately proud of their former greatness, of the splendor that once was Spain's. They continue even now to be conscious of a superiority, the material proof of which vanished 300 years ago with the loss of the treasure found in America. Art and literature were sanctioned by the past and might deal with approved pious subjects. Spaniards might be original in literature and might speak with authority on art, but originality in science was unheard of at that time.

Nevertheless, Cajal began to publish what he saw under his microscope, at first modestly in Spain. Then he determined that to become strong he must struggle against the strong, and he began sending communications to foreign journals. He was looked on with suspicion by his friends. A query ran among the faculty, "Who is this Cajal to pass judgment on foreign authorities?" He began to use silver to stain the finest cellular elements after the method of the great Italian, Golgi. Applying this method with certain practical modifications of his own to the study of the brain, the intricate structure of nerve cells began to

unfold before his eyes. Not having the means to employ an illustrator he drew what his microscope showed him and illustrated his own papers. Here were problems worthy of his greatest effort and Cajal responded with a furious enthusiasm that has never flagged.

He soon observed that foreign workers either ignored his contributions or treated them lightly, and he therefore determined to demonstrate his preparations before the German Society of Anatomists. On arrival in Berlin, he found the members of that society skeptical about his work, rather than curious to see it. But he also saw this attitude change after they had examined his beautiful specimens and seen the nerve cells of the cerebellum as never before, the ascending and descending branches of sensory cells and the termination of the retinal fibers in the optic lobes. That he had scored a triumph in spite of the odds he knew, when Kölliker, the patriarch of German histology, came to him at the close of the conference to praise his work in the highest terms. Before returning to Spain he went to visit numerous German laboratories and discovered, to his surprise, that some of the most justly famous were provided not with good equipment but only with men whose enthusiasm resembled his own.

In 1892, Cajal moved to Madrid with his family to take a professorship in that university. Here he found congenial friends, and in spite of habitual application to his laboratory, he maintained many other interests. He was fond of walks into the open country about Madrid and thought the grays and yellows, the browns and blues of the bare Castilian plain, far lovelier than the unchanging wet green of northern countries. His camera was ever in use on these excursions, and he prepared his own plates for color photographs. Also, after the invariable Spanish custom, he was to be found daily at a certain café in the company of congenial friends who held their "tertulia" there. Over their coffee cups they talked or played chess, and he forgot the problems of the laboratory and gave himself up to a "diastole of rest" in preparation for the day's "systole of work." Yet Cajal's mind, even in periods of rest, was creative, and his diastolic reflections found eventual expression in a charming book called "Coffee House Chatter," just as the hobby of leisure moments gave birth to a book on "Color Photography," which contains many methods that are original in that difficult art.

His scientific publications increased in volume and importance. He elaborated important work on the retina and olfactory lobes and fought for the individuality of nerve cells against the exponents of the reticular theory. Cajal believed in working ever with a guiding hypothesis, although such hypotheses, he said, fall into oblivion, except for those parts of them which are susceptible of scientific proof. He passed

beyond the field of simple structure into theories of the mechanism of thought, association of ideas and attention.

There came an invitation from the Royal Society of London to deliver the Croonian Lecture, perhaps the highest honor he could receive from the English capital. With it was a cordial invitation from Charles Sherrington, already the most brilliant physiologist of England, offering him the hospitality of his home. That lectureship and the honorary degrees received from Oxford and Cambridge were a real triumph for any scientist, and an unheard of thing for a Spaniard.

The visit of this brilliant and eccentric scientist from Spain made a deep impression on scientific London and it was made a feature in the political life of the day. It is told that, during the first week of his stay in the home of Sir Charles Sherrington, Cajal carefully kept the key to his bedchamber with him, saying that he preferred to care for the room himself, but when his hostess finally gained access to the room she found that it had come to look more like a laboratory than a bedroom. There were bottles in the windows, on the chairs and on the floor, perhaps the apparatus of some experiment whose answer he could not wait to know.

When he went from London to Cambridge on the occasion of receiving a degree, a special effort was made to get him to the London station in plenty of time. This too great zeal resulted, however, in his taking an earlier train than the one he was intended to take, so that no one met him at the station in Cambridge. Long after the luncheon which had been prepared in his honor was finished, he was found wandering through the colleges admiring their beauty, unconscious of the consternation that had arisen in the breast of his would-be host.

Recognition of his scientific eminence followed rapidly from foreign countries. The year after the Spanish-American war, Cajal was invited to lecture in the United States at Clark University. It was July when he arrived in New York, the city known in Spain for "its skyscrapers, its avaricious trusts and its heat." He was astonished at the "stern fiber of the Anglo-Saxon race" which impelled even laborers to activity under such a blazing sun. He seemed much interested in American home life and democracy, but he was a little taken aback to see a college professor shoulder his trunk at the station, and when that energetic educator told him that manual labor was considered an obligation in this land of democracy, he observed dryly that he perceived that the abolition of aristocrats was not sufficient to achieve democracy—it was also necessary to develop muscles of steel! Senora Cajal, who accompanied him, looked with disapproving surprise on the new American woman who at that time was bursting into feminism, disapproval in which her husband seems to have shared.

Distinctions rained on Cajal. The International Medical Congress Medal of 1903 was awarded him and this congress met that year in Madrid for the first time. There followed the Helmholtz Prize and the Nobel Prize. These crowning awards were the occasion for felicitations from all over Spain, and he received great ovations from the press, his own countrymen being the last to recognize the value of his work. But in Cajal such things produced a curious mental depression, and he turned with stern determination to attack the problems that lurked beneath his microscope.

The Spanish government is at present building a splendid laboratory in Madrid to be called after him, El Instituto Cajal. It will house the school of biologic research that has sprung up about him. Many pupils are enlarging on his work. Some are impelled, perhaps by borrowed enthusiasm, but others of his race have caught the real spark and are worthy to succeed him. Such brilliant followers as his brother P. Ramón, Tello, Achúcarro, Lafora and, especially, Del Rio-Hortega have achieved international reputations in neurology.

Today, Cajal still works in his laboratory, carrying his seventy-odd years lightly. The old enthusiasm for research still burns within him, though his capacity for sustained effort has decreased. At times he is a little bitter when he sees the scientific world ignoring his past work, and he now publishes the laboratory communication in French in the hope that the voices of his pupils may be less often ignored than his own has been.

Foreign students never seem to have found their way to Cajal's laboratory. The barriers of language and of custom have turned medical men to other countries, and Spain has seemed out of the current of scientific advance. But there is much more than science to be learned from Don Santiago if you search him out in the little café on the corner. There he is wont to sit over his coffee and muse on many things as he watches the changing currents of modern Spain flow through the Plaza de Atocha.

Abstracts from Current Literature

MENINGITIS SYMPATHICA. ISRAEL STRAUSS, Arch. Otolaryng. **3**:46 (Jan.) 1926.

The cerebrospinal fluid may react in the presence of a nearby suppurative process and show turbidity in the fluid, and an increase in pressure, in albumin and in cells, but without the presence of bacteria. Early signs of meningitis may be present. This condition has been termed meningitis sympathica. It is important because prompt operation with removal of the irritating focus will often result in cure. Formerly, the presence of a greatly increased number of cells in the cerebrospinal fluid was considered definite evidence of meningitis and operation was frequently deferred because it was considered hopeless. Bearing in mind this new conception that the fluid reacts to a toxic state and may not be the seat of active suppuration, a great many patients will be saved. Nine cases are reported in detail of which the following may be quoted:

CASE 1.—*Meningitis sympathica in a case of otitis media without clinical signs of mastoiditis.* A child was admitted to the hospital complaining of pain in the right ear with discharge for three days. Physical examination revealed a rigid neck, bilateral Kernig sign and positive Brudzinski sign. Before operation 5 cc. of slightly turbid fluid under increased pressure was removed; this contained 1,100 cells per cubic millimeter, of which 85 per cent were polymorphonuclear leukocytes, but no bacteria. There was a slight amount of pus in the mastoid cells; an area of the dura the size of a nickel was exposed, which appeared yellowish, gray and thickened. Recovery followed.

CASE 2.—*Old otitis media with no clinical signs of mastoiditis but a thrombosis of the lateral sinus giving rise to symptoms of meningitis sympathica.* A child was admitted with a diagnosis of mastoiditis with meningitis and septicemia. Two months before admission the ear was incised and discharged freely. The discharge ceased until two weeks before admission when the ear was again incised. There was headache but no pain behind the ear. Physical examination revealed no abnormality in the eyes, but a moderate rigidity of the neck suggestive of a bilateral Kernig sign. The preliminary diagnosis was acute meningitis. Lumbar puncture yielded 35 cc. of cloudy fluid containing: 2,000 cells per cubic millimeter; albumin, 4 mm. ring; globulin increased; no tubercle bacilli or other bacteria in direct smears or cultures. Ninety per cent of the cells were of polymorphonuclear type, and 10 per cent were lymphocytes. The left mastoid was exposed, but no inflammation was found; the dura was then exposed in both the middle and the posterior fossa, but no pathologic process was seen. The sinus was exposed and a thrombosis was discovered. The jugular vein was ligated. The same day lumbar puncture yielded 40 cc. of cloudy spinal fluid; 13,440 cells per cubic millimeter; 95 per cent polymorphonuclear cells; 5 per cent lymphocytes; albumin, 5 mm. ring; globulin increased. The Wassermann reaction was negative. Direct smears showed many pus cells but no bacteria. Blood culture taken before operation was negative. The patient was discharged as improved. Subsequently, he was readmitted to the hospital, a radical mastoid was done and a cholesteatoma removed. He was then discharged as cured.

CASE 3.—*Meningitis sympathica in a youth who had not only been operated on for acute mastoiditis and sinus thrombosis, but in whom infection of both lateral sinuses had persisted despite the operation, with persistence of meningitis*

sympathica but without the development of an acute operative meningitis. The spinal fluid showed slightly increased pressure with 150 cells, mostly lymphocytes. There was a history of operation, six months before admission, for mastoiditis and sinus thrombosis followed by persistent headache. A necropsy revealed no evidence of meningitis. Both lateral sinuses at the tentorium were filled with pus.

CASE 4.—*Meningitis sympathica with both mastoiditis and labyrinthitis.* A patient, aged 26, complained of pain in the left ear for four days and of discharge for one month. Two weeks before admission she had attacks of vomiting, staggering and dizziness. Examination on the day of admission revealed a granuloma springing from the right ear, but no neurologic signs. Under increased pressure 5 cc. of turbid spinal fluid was removed which contained 4,400 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. January 30, total deafness of the left ear developed. There was no caloric reaction. Definite rigidity of the neck and a bilateral Kernig sign were present. Spinal fluid was removed under increased pressure, and contained 6,400 cells per cubic millimeter, 90 per cent of which were polymorphonuclear cells; no bacteria were found in cultures. February 4, there was paresis of the upper branches of the left facial nerve and the fluid showed 1,200 cells per cubic millimeter, many lymphocytes and no bacteria. A radical mastoid operation and labyrinthectomy were performed. Facial paresis was absent. The patient was discharged as cured.

CASE 6.—*Meningitis with the focus of infection in a chronic ear and mastoid inflammation.* The inflammation of the ear and the mastoid cells had resulted in the development of an abscess, and the reaction of the spinal fluid indicated the presence of an intracranial complication demanding intervention. Unquestionably, had the spinal fluid been examined earlier in the course of the disease, changes in this fluid would have been noted and earlier operative intervention undertaken. The result might have been more favorable. The patient was admitted to the otologic service Nov. 8, 1918, with the complaint that five weeks before admission, following the removal of a polyp from the right ear, severe pain on the right side of the head developed, with a continuous temperature of 104 F. The patient appeared septic, complained of dizziness on attempting to stand, and also vomited several times. Physical examination revealed a slight right facial weakness, marked nystagmus to the right, moderate nystagmus to the left, bradycardia and marked adiadokokinesis. November 10, exploratory mastoidectomy, craniotomy and decompression were performed. The mastoid showed ivory-like hardness with complete obliteration of the mastoid cells. No exudation existed about the sinus, nor on the dura of the temporal fossa. The antrum of the ear was large and filled with pus. The squamous portion of the temporal bone was denuded, and the dura was exposed over an area 1½ inches (4 cm.) in diameter; pressure was markedly increased, but the dura was clean with no exudation. Lumbar puncture produced clear fluid under moderately increased pressure, with 300 cells, 80 per cent of which were of mononuclear and the remainder of polymorphonuclear type; smears and cultures were negative; the albumin ring was 4 mm. November 11, slight bilateral papilledema was reported, and on the same day craniotomy with drainage was performed. The skull and dura were opened over the cerebellum; a grooved director located an abscess cavity in the cerebellum, which was drained. Smears from the pus showed the presence of gram-positive cocci; cultures yielded *Staphylococcus aureus.* The patient died on the night of the second operation.

It frequently happens in cases of acute otitis that either while the acute process is still present or after it has subsided and even the perforation of the tympanum has healed, symptoms of meningitis develop. A lumbar puncture at this time shows increase in pressure of the spinal fluid and the presence of a large number of polymorphonuclear leukocytes. When examined by culture or by smears, this fluid appears to contain no bacteria. A number of days may elapse during which the symptoms of meningitis persist and are aggravated, and yet no bacteria are found in the spinal fluid after repeated examination.

Finally, a day or two before death, which is the usual outcome of a case of this kind, bacterial growth is obtained. Cases such as this are not to be regarded as meningitis sympathica, but as instances in which, for some reason as yet unknown, bacteria cannot be demonstrated in the spinal fluid. It is possible that the organisms are present in the meninges but not free in the fluid; that the few which do enter the fluid are disintegrated by bactericidal action and that a period elapses until the organisms become so abundant that the bactericidal power of the cells lining the subarachnoid space is unable to cope with the invasion, and the germs can then be demonstrated. These cases must be regarded from the onset as cases of acute meningitis; they have not the significance of meningitis sympathica.

Meningitis sympathica occurs when there is a brain abscess and, whether such an abscess is associated with an inflammation of otitic or accessory sinus origin, it is always a symptom of grave portent. It is an indication that the inflammatory focus is not under control, and unless this focus is adequately attacked, acute meningitis is certain to intervene, or in a case of brain abscess the patient will succumb to the inflammatory process.

HUNTER, Philadelphia

THE PATHOGENESIS OF ATTACKS OF MIGRAINE AND ITS RELATION TO EPILEPSY. HUGO RICHTER, Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:387 (July) 1925.

Two problems arise in dealing with the pathogenesis of migraine. The first is as to the nature of the pathologic-physiologic process in the brain, or in a segment of the brain, during an attack of migraine. The second question is whether there is a specific make-up of the territory affected which leads to migrainous attacks. Hohn and Stein believe there is a migrainous constitution; others believe in a disturbance in the glands of internal secretion, while more recent investigators have favored a toxic origin for the attacks, an autointoxication. The question of etiology in migraine is as fraught with difficulties as in epilepsy.

The pathogenesis of hemicrania made a great step forward after Pol's observations on the clinical significance of vascular spasms. Pol included under this term many hitherto obscure clinical conditions and united them in one group. The pathogenesis of these conditions was found in a local ischemia as a result of a vascular spasm and insufficient blood supply. This phenomenon, in Pol's conception, affected two areas particularly: the cerebral and the abdominal vessels. These observations were followed by Dubois' theory of migrainous attacks. This consisted merely in the belief that migraine was due to a local or general spasm of the cerebral vessels as the result of a vasomotor activity. Up to now, however, no definite proof has been forthcoming that this is so, although Charcot and Dubois brought evidence to show that there was a sympathicotonic effect in many cases of migraine as evidenced by the ocular symptoms. Richter reports a case of hemicrania in

which, during an attack, the pupil on the side of the attack dilated, returning to normal after the attack. This does not occur in the majority of cases, however, and cannot be taken as absolute proof of the vasomotor sympathicotonic theory. On the other hand, there occurs at times in migraine a sympathetic paralysis which is transitory and evidenced by myosis and flushing. Möllendorf has called attention to this sympathicoparalytic form of migraine.

Is the angiospasm which occurs in migraine general or local? If local, it should have localizing stigmas. Because of the absence of loss of consciousness and tonic-clonic spasms the spasms cannot be localized in the motor cortex. In this respect, incidentally, migraine differs from epilepsy which includes characteristically a loss of consciousness and convulsions, either jacksonian or general. There are cases of migraine in which undoubtedly there is a generalized vascular spasm. Definite localizing signs can be adduced in migraine, for besides the subjective complaints of headache, vomiting, etc., one commonly finds definite objective phenomena. Indeed so common are these that clinically migraine is divided into several different types — ophthalmic, ophthalmoplegic, hemiplegic, etc.

On the basis of 300 cases seen over a period of three years Richter produces evidence to show that local angiospasms occur in migraine. In the first place, lesions of the oculomotor nucleus occur. Richter describes a case with right-sided hemicrania and right oculomotor paralysis (ophthalmoplegia externa), another with a similar condition and a partial trigeminal paralysis, and a third case with left hemicrania, left oculomotor paralysis. Flatau in his monograph describes the involvement of the third nucleus in its various forms in migraine. The cases of Richter differ from those in the literature in being cases of ophthalmoplegia externa rather than ophthalmoplegia totalis. Richter believes the lesion in these cases is due to an involvement of the oculomotor nucleus through a spasm of the radicular arterioles supplying this nucleus.

Lesions of the facial nerve also occur in migraine. Richter describes a case with right hemicrania, with right oculomotor paralysis, and later with right hemicrania and hemiplegia alternans facialis, also another case with right hemicrania and right peripheral facial paralysis. He places the lesion or spasm in the nucleus or in the intracerebral course of the cranial nerve. Bernhardt first called attention to this condition. He showed that in recurring facial paralysis the onset was often accompanied by an attack of headache, or that the latter was soon after followed by facial paralysis. He named the syndrome hemicrania facioplegia. Cases of involvement of the facial nerve and of the eye muscles have been reported by Mingazzini, Paderstein, and others.

Paralysis of the abducens is also common in migraine. Three cases are reported with left-sided hemicrania and a left abducens paralysis. This form of hemicrania has been described by Bernheimer, Armerod, Marina and Bornstein. Luzenberger and Bornstein report a paralysis of the trochlear nerve in migraine. A case of trigeminal paralysis is reported by Richter, the patient having also a paralysis of the abducens, hypoglossus and sympathetic center. The case occurred in a man with lead poisoning. According to Flatau involvement of the trigeminus is one of the most common phenomena in migraine. Paresthesias, hyperesthesias and hypesthesias are often described, usually not involving the entire trigeminal distribution but one of the roots. Richter reports three cases with trigeminal affection. He also describes a case of hemicrania with hemiplegia and aphasia; there was no loss of consciousness and no convulsions. Clark followed through three generations a family with hemicrania in which hemiplegia and aphasia developed, the latter always motor and asso-

ciated with either right or left hemiplegia. The pyramidal tracts, in Richter's opinion, are involved in their infracortical portions, while the aphasia in practically all cases is purely motor.

Disturbances in vision are extremely common. Flatau differentiated two groups: (1) simple, transitory disturbances in vision from partial to complete amblyopia, scotomas and hemianopia; (2) disturbances of a shimmering, spectral nature with bright figures, streaks of light, etc. Most authors place the lesion in these cases in the calcarine cortex. Keller described a case of migraine with hemianopia in which the pupillary reaction was intact on the hemianopic side, showing that the lesion was between the oculomotor nucleus and the occipital cortex. Raullet described a case of tabes with optic atrophy with disturbances of Flatau's second group. On the other hand, some authors hold that the disturbances in vision in migraine are due to disturbances in the retina. Richter says the trouble is in the visual cortex or in the central tract between the cortex and the third nucleus.

Richter's conclusion is that in hemicrania an angiospasm occurs in the region of the blood supply of the vertebral system.

On the other hand, in epilepsy, contrary to what is found in migraine loss of consciousness and convulsions occur. Redlich remarks on cases of migraine developing epilepsy after the cessation of the former, and vice versa. The two disturbances are similar in their onset in early life, their course, the occurrence of aura, the occurrence of prolonged attacks (status epilepticus and status hemicranicus) and their amelioration by bromides and phenobarbital. They differ as pointed out above. In epilepsy, however, the motor cortex is involved, whereas in migraine it escapes. The angiospasm in migraine involves the vertebral arteries and the inferior cervical sympathetic ganglia, whereas in epilepsy it involves the carotid and the superior cervical ganglia. In the conception of Pol, therefore, migraine and epilepsy represent two types of vascular crises affecting different vessels and different areas.

ALPERS, Philadelphia.

CLINICAL RESEARCH ON THE ORIGIN OF NEURITIS OF THE OPTICAL NERVE WITH ESPECIAL REFERENCE TO ITS RELATION TO MULTIPLE SCLEROSIS. ELSA FRIEDINGER, Schweiz. med. Wchnschr. **55**:1093-1097 (Nov. 26) 1925.

As is well known, eye changes are of the utmost importance in the early diagnosis of multiple sclerosis. Much progress has been made in the last thirty years in the study of this disease. Many cases of inflammation or atrophy of the optic nerve that would have been looked on as syphilitic in the pre-Wassermann reaction times have been recognized as early symptoms of multiple sclerosis. With the knowledge that early fundus changes meant multiple sclerosis, a tendency developed to make such a diagnosis if the Wassermann reaction was negative, even when there was but slight basis for it. Only in the last decade, since it has been proved that tuberculosis may occur in the optic nerve, has the possibility of such a condition been considered. It is not unusual to see a typical disseminated chorioiditis of scrofulous origin coexistent with optic neuritis, and it is not always possible in such cases to associate it with a purely secondary disease of the retina and optic nerve.

The author has gone through the journals of the Zurich Eye Clinic of the last ten years, from 1914 to 1923, and so far as possible etiologically, has sorted the material and checked up the cases of doubtful etiology. There were 504 cases of optic affections among which were 238 patients with optic neuritis, 187 males and 51 females. In 168 cases the cause could be determined, 146

males (this high figure is due to the frequency of toxic retrobulbar neuritis) and 22 females. Of the seventy cases of uncertain etiology, only those are again mentioned that the author personally was able to check up or received reports on. Of these there were twenty-six cases.

The author has undertaken to show how often multiple sclerosis developed in the course of years out of a case of neuritis of unknown genesis. Twenty-six cases are cited in detail; they are divided into two groups. The first group includes nineteen patients who were known to have had optic neuritis of unknown etiology. Thirteen of these were examined by a neurologist. Of the others, four are doing strenuous work and insist that they feel well. A cursory examination in the eye clinic revealed no reflex anomaly and no disturbance of speech or gait, but since a thorough examination was not made these cases must remain doubtful.

In the entire first group only one case could be diagnosed as multiple sclerosis. Only two of the second group were positive. Of these twenty-six patients, three developed multiple sclerosis. It is assumed that perhaps a later checking up would reveal multiple sclerosis in others. The author remarks that nothing positive could be found in patients whose neuritis occurred more than five years previous to this checking up.

From this same material the author sorted out cases of definite multiple sclerosis in order to ascertain how often a diagnosis was made on eye symptoms, how often patients with the finished diagnosis were referred for eye examinations and how the two groups compared. Twenty patients with definite multiple sclerosis went through the polyclinic between 1914 and 1923. Eight of these patients were referred from other clinics or private physicians for confirmation of a diagnosis based on positive eye findings. In this group, eye findings were in the background and were less disturbing than other symptoms of the disease.

In 60 per cent of the entire group (twelve cases), multiple sclerosis was presupposed and the diagnosis confirmed by special examinations. In this group the subjective symptoms were more frequent. There were observed:

Difficulty in close vision	1
Blurred vision	2
Pain on bulbar movement	2

Objective changes noted were:

Ptosis, complete	1
Nystagmus	1
Diminution of vision	3
Optic atrophy	6
Defect in field of vision (1 contraction of field, 3 central scotoma, 1 enlargement of blind spots)	5
Former neuritis	1

The author states that the results of her investigation do not correspond with those of others as she did not find so large a percentage. Fleischer, who undertook the same sort of investigation in forty-two cases, reported a positive neurologic result in two thirds of his cases. There was a longer interval between the neuritis and the neurologic checking up in more than half of Fleischer's cases. Friedinger has not included doubtful cases in her report.

The conclusions reached are: As heretofore, in dealing with optic neuritis of unknown etiology (intra-ocular and retrobulbar), the eye specialist should take the nervous system into consideration, but it must not be assumed that multiple sclerosis, which may appear after a longer or shorter period of time, will explain the present neuritis. Such an outcome is not as frequent as was

formerly believed. Today, signs of general infection of tuberculous origin, as evidence of local tuberculosis of the eye, should be looked for in these cases. In the material checked up a number of cases had definite connections with tuberculosis.

From the "Handbuch der Neurologie des Auges" by Wilbrand and Sanger, may be quoted: "Certain forms of neuritis of unknown etiology have in themselves a good prognosis, at least for the eye, but not for the general condition, as these are frequently forerunners of a multiple sclerosis." Contrary to this the author states that a certain number of cases are of tuberculous origin, so that the prognosis need not be feared.

MOERSCH, Rochester, Minn.

A CONTRIBUTION TO THE STUDY OF "EXPRESSION MOVEMENTS" OF MENTAL AND PHYSICAL PAINS IN THE BODY AND EXTREMITIES. EKLYSIS REFLEX OF MENTAL PAINS. JENO KOLLARITS, Schweiz. Arch. f. Neurol. u. Psychiat. **17**:63-73, 1925.

In the study of this problem Kollarits contented himself by making notations of involuntary movements observed by him in other people and in himself when placed under emotional stresses. A registration of these movements by some mechanical device would be more accurate, but this would be difficult and probably would yield nothing more than would simple observation.

This investigation was inspired by the reading of an article published by a European layman who had negroes under his control. This person stated that whenever he questioned any of his black undressed laborers he made it a point to observe their feet. In case the great toe of the negro was elevated while he was talking, the overseer was convinced that the negro was lying. Shortly thereafter Kollarits observed this "lying reflex," accompanied by dorsiflexion of the ankle, in himself. At the time this occurred he was busily engaged in his work, when some one asked him a question. He flung a careless "yes" at the interrogator, noted with some surprise the movement of his foot, and then appreciated that this answer did not fill all requirements. A little further observation convinced the writer that these movements were not "lying reflexes" but were an expression of some physical or mental pain.

Among the various causes noted, some of the following may be mentioned: being embarrassed at inability to answer a question, passing an acquaintance whom one does not wish to greet, noting that some one else has carried out a duty that one should have attended to oneself, being dissatisfied with one's own work, reading of an unfortunate occurrence, being questioned about a diagnosis of which one is uncertain, being troubled during work by unnecessary questions, being placed under scrutiny. Among the physical causes the following were noted: a distended bladder, earache, painful coughing, a stitch in the side.

The following were some of the movements noted in 500 cases. Dorsiflexion, particularly of the right great toe and of the foot, 109 times, dorsiflexion of the left great toe sixty-two times, dorsiflexion of both great toes and feet sixty-four times, plantar flexion of the right foot and right toe sixteen times, similar movements of the left foot three times, similar movements of both feet eleven times. Other movements included rotation of the lower extremities, elevation of the heels, movements of the upper extremities, shoulders, trunk, hands and head.

The more painful the sensation, the more extensive and protracted were these movements. Movements of the lower extremity appeared to be more frequent even than mimic movements of the face. These observations are of interest in view of Wundt's statement that "the muscles employed in walking are

generally brought into play only with the strongest affects." Kollarits believes that this is an error based on incomplete observation. The movements are heightened under the influence of cold; they are more marked in children than in adults; they depend somewhat on the character of the person.

The involuntary movements which accompany psychic and physical distress are similar. This is particularly true when the physical pain arises in the viscera. It is noteworthy that in physical pain the movements resemble the shortening reflexes observed in lesions of the pyramidal tract. Wundt is of the opinion that three principles underlie movements of expression. These are: first, the principle of direct change of innervation; second, the principle of association of related emotions, and third, the principle of the relationship of movement to sensory perception. The writer does not believe that it is necessary to attribute such great importance to the psychologic factors involved in the association of related feelings and the origin of local sensations. The organism is concerned not only with the resistance of attack on some particular part of the body but also against attack on the entire organism which may follow danger to some isolated member. It would not be practical if the specialization of the nervous system had advanced to such a point that reactions of expression should not become generalized.

WOLTMAN, Rochester, Minn.

TUMOR OF THE PETROSPHENOIDAL ANGLE OF NASAL ORIGIN. J. A. BARRÉ and R. STOEBER, Rev. d'oto-neuro-ocul. **2**:81 (Feb.) 1924.

This report concerns a man, aged 35, whose death was caused by a malignant myxoma of the nose, which had extended into the endocranium and had produced metastases in the lymph glands of the neck and in the suprarenals. The train of events was: (1) anesthesia and then pain in the domain of the three branches of the left trigeminus, particularly the superior and inferior maxillary branches; (2) exophthalmus of the left eye and marked venous dilatation in the temporo-orbital region; (3) submaxillary adenitis, nonmalignant in character; (4) diminished hearing in both ears; (5) paresis of the left third and fourth cranial nerves; (6) diminished vision of the left eye but no modification of the visual fields; (7) hypersensitive vestibular reactions on both sides; (8) minimal participation of the left facial nerve.

Left ethmoiditis and a nasal polyp were found. There was no increase of intracranial tension. The cerebrospinal fluid contained albumin and an increase in cells. Clouding of the outlines of the sella turcica was shown in the roentgenogram. Negative findings were obtained from other examinations. The Bordet-Wassermann reaction was negative in the blood and spinal fluid. Biopsy of the submaxillary gland revealed no neoplasm.

At necropsy an intracranial tumor was found occupying the internal part of the middle cranial fossa (petrosphenoidal angle) and covering the cavernous sinus. It was part of a tumor of the left posterior superior nasal cavity which had invaded the skull by infiltration of the ethmoidal and sphenoidal sinuses and penetrated in front of the anterior lacerated foramen. The left cavernous sinus was infiltrated by the growth. It extended backward over the petrous bone to the margin of the internal auditory meatus. The left deep cervical gland showed a diffuse endothelioma, and the suprarenal glands showed epithelioma.

The order of appearance of the symptoms gives some clue to the diagnosis, indicating a process extending from without into the skull. Certain conditions cannot be explained: the absence of increased intracranial tension in the presence of exophthalmus and dilatation of the orbital veins; the absence of

edema of the eyegrounds in the presence of involvement of the cavernous sinus and the establishment of effective collateral circulation. Examples of intracranial tumors without increased intracranial pressure or papillary edema are well known. The authors think that certain facts of pathologic physiology of the intracranial circulation are not known and that the study of its mechanism may clear up the question of increased tension.

No histologic change in the tumor resulted from the use of roentgen-ray treatment. The findings in the cerebrospinal fluid did not help in differentiating between a thrombophlebitis of the cavernous sinus and an intracranial tumor. The fact that a superficial gland, removed at biopsy, was healthy and a neighboring deeper one, removed at necropsy, was neoplastic, should teach us to remove glands from as great a depth as possible for study during life.

In the differential diagnosis between tumors of the petrosphenoidal angle and hypophysial tumors, the authors point out that the latter cause hemianopia, unilateral or bilateral, and produce pituitary disturbances (acromegaly, giantism, genital changes, etc.), excavate or enlarge the sella and compress the cavernous sinus; diplopia appears before neuralgia, which is quite rare and usually begins in the ophthalmic division. The former causes no hemianopia nor skeletal disturbances; vague modifications only of the sella (blurring in the roentgenogram), which retains its normal dimensions; early facial neuralgia, beginning in the inferior maxillary division, and late diplopia; all signs are strictly unilateral.

DENNIS, Colorado Springs, Colo.

THE INVOLUNTARY NERVOUS SYSTEM: AN IMPORTANT FACTOR IN THE BODY'S RESISTANCE. ERNST FRIEDRICH MULLER, Arch. Int. Med. **35**:796 (June) 1925.

Infection and body resistance have been studied for several centuries and nonspecific therapy has been practiced for an equal length of time. Nonspecific therapy stimulates body resistance and it is the purpose of the author to determine the physiologic basis of this resistance, the organs of resistance and how they function. Theoretically, resistance is a product of the functions of various organs, but under healthy conditions this resistance is latent and becomes apparent only when some abnormal process exists. Two groups of organs are apparently involved: the bone marrow system and the involuntary nervous system. It also encompasses the conduction of the stimulation to the bone marrow system and of the newly formed immunizing substances and leukocytes to the site of the stimulus.

The vascular system is accepted as embodying the manifest and measurable activity of the involuntary nervous system. Vasodilatation and vasoconstriction are normally in balance, but this relation can be altered by stimulation of one or the other. The paths involved as a result of this stimulation are not known. The midbrain, the optic thalamus and the central gray matter of the third ventricle are places in which sensory stimuli and stimuli resulting from changes of mood pass over to vasoconstrictor channels. Vasodilatation and vasoconstriction can be artificially caused by alkaloids. Vasodilatation is also caused by inflammatory irritations, this being probably due to a local reflex.

Intravenous injection of peptonoid bodies results in a great diminution in leukocytes, especially the polymorphonuclear cells, in the peripheral blood; they are supposedly retained in the vessels of the inner organs. The same sort of reaction, though milder in character, may be obtained by ingestion of

milk on an empty stomach. The apparent leukopenia is explained as due to a disturbance of the involuntary nervous system, and this is represented by an acute displacement of the leukocytes.

Stimulation of the surface of the body has the opposite effect, causing vasodilatation at the point of stimulation by excitation of the parasympathetic system. The stimulus is greatest if intradermal, less if subcutaneous, and least if intravenous; this, apparently, is true regardless of the type of stimulus used. The change in tonus of blood vessel walls allows or causes an increase in number of leukocytes at the point of stimulation. At the same time changes take place in the myeloid system, more especially in the bone marrow of the long bones. This is undoubtedly due to stimulation from the parasympathetic system and results in great dilatation of the vessels, followed by increased vascularization and later by the appearance of myeloid elements and of leukocytosis. The involuntary nervous system may then act by conducting the newly formed leukocytes to the point of stimulation or infection where they are retained. There are then produced symptoms of local inflammation. The resistance of the body is thus partially due to the action of the involuntary nervous system.

WAGGONER, Philadelphia.

INFLUENCE ON NERVES IN KIDNEY FUNCTION IN RELATION TO PROBLEM OF RENAL SYMPATHECTOMY. L. F. MILLIKEN and W. G. KARR, J. Urol. **13**:1 (Jan.) 1925.

The nerve supply of the kidney is derived chiefly from the renal plexus, which is a nervous network about the vessels of the renal pedicle, the fibers of which follow the renal vessels to their finest ramifications even as far as the capillaries. The vagus also sometimes sends a branch direct to the kidney but there is no evidence that it affects the secretion. The influence of the renal nerves is chiefly vasoconstrictor; stimulation decreases the secretion of urine; depression or section increases it. A review of experimental work on kidney denervation, from Claude Bernard to recent workers, has proved this definitely. Many observers, Carrel and Guthrie, Lobenhoffer, Zaaiger Boeminghaus, Marshall and Kolls, have shown that innervation of the kidney is not essential to function and it is known that excretion continues years after all connection with the central nervous system has been divided. Marshall and Kolls have shown that the denervated kidney secreted thrice as much as the normal kidney. No one, however, has as yet proved the existence of secretory fibers in the renal plexus or splanchnic nerves.

The authors, by denervating one kidney only, have studied its functions by cystoscopic methods in dogs. Indigo carmin was injected intravenously and was observed to appear from the operated side in from thirty to ninety seconds sooner than from the normal side. The jets from the operated side came in some cases twice as often and were projected farther across the field, but were not as deep blue as those from the normal kidney. Under ether anesthesia it was observed that the function of the normal kidney was inhibited, while that of a denervated kidney was not influenced. One bitch gave birth to and suckled a litter of pups seven months after bilateral kidney denervation. Large amounts of normal salt solution, 5 per cent and 10 per cent solutions, were injected intravenously to discover if kidneys deprived of their nerve supply could meet demands of unusual emergencies. Practically all of the injected salt was removed by the kidneys in from five to seven hours; the denervated kidneys thus appeared as efficient as the normal, contradicting the objection of Noennecke that a denervated kidney cannot take care of unusual emergencies.

Theoretical considerations lead the authors to suggest that denervation is the logical procedure in reflex anuria, or oliguria produced by spasm of the renal vessels due to reflex stimulation of the vasoconstrictors. Denervation of the kidney by Papin and Ambard has relieved nephralgia in two cases. Inasmuch as denervation increases the blood supply incident to increased function of the kidney, it might act favorably in renal tuberculosis. Likewise, by causing a better flushing of the kidney by a more dilute urine it might prevent the reformation of renal calculi. The operation is also suggested as a substitute for or adjunct to decapsulation, when the latter operation is apt to produce excessive cicatrization. The authors recommend median abdominal or longitudinal rectus incision as enabling a quicker operation than if done by the lumbar incision—and all investing tissues of the renal vessels from their junction with the vena cava and aorta should be stripped toward the kidney, thus to enable all fibers of the renal plexus to be removed along the entire course of the vessels. No untoward results follow the operation even when both kidneys are denervated at the same time.

HART, Philadelphia.

THE IMPULSES PRODUCED BY SENSORY NERVE ENDINGS. E. D. ADRIAN, J. Physiol. **61**:49-72 (March 18) 1926.

The paper describes a combination of a capillary electrometer with a three valve amplifier capable of recording rapid changes of potential of 0.01 millivolts. Afferent action currents have been recorded from several different nerves of the frog, the rabbit and the cat. It is probable that many of the oscillations represent action currents of a single nerve fiber, and these have the same form and time relations (allowing for temperature differences) in all cases. There is no evidence that an increase in the stimulus increases the size of the action currents in single fibers, but the frequency of the impulses in the nerve trunk increases and leads to interference and overlapping of the oscillations recorded. When a muscle is stretched by a weight, the discharge of afferent impulses continues for as long as ten minutes provided the tension is maintained. Similarly, the passage of impulses up to the vagus continues if the lungs are held in the expanded state. No evidence was found of renewed discharge of impulses in the vagus on deflation of the lungs.

IMPULSES FROM A SINGLE SENSORY END-ORGAN. E. D. ADRIAN and Y. ZOTTERMAN, J. Physiol. **61**:8 (March 18) 1926.

The same technic was employed as in the preceding paper. The sternocutaneous muscle of the frog was used which has at least one muscle spindle, action currents being recorded from its nerve which contains only from fifteen to twenty fibers. Stretching gives irregular action currents at 100 a second or more. Cutting away successive strips of the muscle reduces the frequency and one or more definite rhythms appear. Each regular series is interpreted as the response of a single end-organ. The frequency of such series varies from 10 to 50 a second increasing with the strength of the stimulus. The magnitude of oscillations remains constant. By recording frequencies with stimuli of different strengths, recovery curves were constructed. These have the same form as that of the nerve fiber but are from five to ten times as long. The continuous discharge to a constant stimulus is ascribed to slow adaptation.

It would be hard to exaggerate the possibilities of this technic or the importance of the results already obtained. For the first time it has been

demonstrated that increase of intensity of stimulus results in increase of frequency of afferent impulses leaving each receptor, confirming a suggestion made years ago by Forbes on the basis that the number of receptors and afferent fibers was insufficient to account, on a basis of variation in number of fibers involved, for the gradations in intensity that may be perceived. The frequencies observed are surprisingly low — far lower than the limits imposed by the refractory period of nerve fiber. Apparently the receptors studied in frog muscle contain a transmitting apparatus with an absolute refractory period of about 0.02 second and a relative refractory period of about 0.1 second.

McCouch, Philadelphia.

Evidence of Nervous Control of Leukocytic Activity by the Involuntary Nervous System. Ernst F. Mueller, Arch. Int. Med. **37**:268 (Feb.) 1926.

The problem is presented as to what power impels the migration of leukocytes from their site of production to an infected area. Having ascertained in other studies that peptone, and even salt solution or distilled water, can cause a peripheral leukopenia, the next step was the observation that such a leukopenia did not develop in certain cases of skin disease.

Starting with this, the author found that the intradermal injection of minute quantities of albumin caused a pronounced drop within a few minutes. This, he believes, is due to a relationship existing between the skin and the autonomic nervous system. For, by blocking the nerves carrying parasympathetic stimuli to the splanchnic region, i. e., vasodilators, it was not possible to secure this leukopenia. Epinephrine by sympathicomimetic action, and atropine by its induction of parasympathetic paralysis, alike prevent the manifestation of peripheral leukopenia.

The cause of this splanchnic "reservoir" action is as yet purely hypothetic; possibly some chemical or electrical relation between the vessel wall and the circulating cells.

However, the splanchic element is not the sole factor, for the work of Embden and Freundlich is cited, showing that the leukocytic drop does not occur in the peripheral vessels of an extremity which has had its vessel nerves severed; even when the injection is given elsewhere in the body. In other words, parasympathetic "overbalance" induces leukocytosis; sympathetic overbalance disposes to leukopenia. This perhaps, then, means that the skin and splanchnic region are systems normally in fine balance, and under a unit nervous control.

As evidence it has been shown that in diabetes, insulin shock occurring with abrupt blood sugar lowering is simply a manifestation of cutaneous parasympathetic stimuli, i. e., dilatation and leukocytosis. In this case the usual physiologic balance has been reversed.

In summary the author considers the nerve control of leukocytic activity to have been definitely proved.

Anderson, Philadelphia.

Photographed Lilliputian Hallucinations. Edmund S. Conklin, J. Nerv. & Ment. Dis. **62**:133 (Aug.) 1925.

The author describes the case of a man of common school education and of marked religious interests who is said to have had hallucinations of diminutive figures since childhood. On closing his eyes the perspective seemed to broaden out into a distant horizon on which tiny forms, of human or animal character, moved about gracefully. He felt the imprint of soft hands on him,

curling or pulling his hair. To the patient these things imported a proof of immortality, and to extend his convictions he constructed a camera with which he took photographs of "the spirits." By examination of the prints with a lens he found a vast variety of little figures which could not be seen on casual examination; but when the print was placed against a lighted window perceptive illusions of the expectant variety could be obtained. The hallucinations were all diminutive, active and agreeable. The author considers that the peripheral stimulus for these hallucinations was idioretinal light — a phenomenon not infrequent in hypnogogic states. The variability in size of the hallucinated figures recalls the variation in the size of visual after-images with the distance of the field of projection. Substitution of some process, as idioretinal light, for a visual after-image would render the projected image less influenced by the proportion of the field into which it was projected. Later the patient came to see his figures with eyes open in daylight, but not without difficulty at first. Perret's psychanalytic explanation of the diminutive size of these hallucinations on the grounds that they are an escape from persecutory reality seems less applicable in this case than that of reversion to the child stage in which constancy of magnitude of figure images is imperfect. Such constancy is a result of acquired syntheses in the process of maturation, and these syntheses may, in the author's opinion, be broken up by organic or psychogenic factors. In this case the break up of the syntheses seems to have been gradually self-indirect. The author favors the theory that the agreeableness is due to the fairylike nature of the images.

HART, Philadelphia.

RADIOTHERAPY AND RADIODIAGNOSIS OF CEREBRAL TUMORS. GABRIELLE LEVY, Rev. neurol. **1**:550 (Nov.) 1925.

This work is the result of the personal experience of the author and of previous writers. The conclusions are of practical interest and may be summarized as follows: Radiotherapy should be applied to deep, diffuse tumors, particularly to gliomas; to intraventricular tumors, and especially to tumors of the hypophysis. This form of treatment is contraindicated in tuberculomas, gummas and small tumors that are easily enucleated surgically. Before instituting radiotherapy, it is essential to determine whether there is choking of the disks; when the optic nerve is threatened a preliminary decompressive operation should be performed. In the absence of papilledema, roentgen-ray treatment may be applied, beginning with a small dose, and controlling its continuation by neurologic and ophthalmoscopic examinations. If papilledema appears during the course of treatment, the roentgen-ray dose must be diminished or even discontinued. Some authors, including Bremer and Jungling, advise a decompression operation in every case before applying roentgen rays because of the strong probability of the development of a secondary hypertension.

When the location of the tumor is known, the roentgen rays should be centered on the tumor. If the location of the neoplasm has not been determined it is permissible, with caution, to radiate the whole skull by successive fields. There are no indications of the destruction of the tumor except clinical recovery; malignant tumors may recur after radiotherapy as after surgery. When recurrence occurs the roentgen-ray treatment may be repeated. Levy believes that roentgenotherapy, applied with proper precautions, is less dangerous than surgery and will probably acquire a more extended field of application with improvement in technic.

FERRARO, Washington, D. C.

THE SPINAL FLUID SUGAR IN ENCEPHALITIS. J. L. HALLIDAY, Quart. J. Med. **18**:300-308 (April) 1925.

The author reports four series or groups of cases in which the blood sugar and spinal fluid sugar were studied. Series 1 consisted of twenty-five specimens of blood and spinal fluid from twenty-one cases of encephalitis taken after twelve hours of fasting. The blood sugar averaged 0.095 mg. per cent. Series 2 consisted of six spinal fluids taken prior to spinal anesthesia. The glucose in these specimens averaged 0.057 mg. per cent. Series 3 consisted of fifteen cases (twelve reported as encephalitis) in which the blood was taken after twelve hours of fasting and the spinal fluid for glucose estimation from two to three hours after a dose of glucose had been given by mouth. In this group the sugar content of the spinal fluid averaged 0.015 mg. per cent, higher than in series 1. In series 4 the author reports the results of the examination of the blood and spinal fluid from three cases of encephalitis taken for glucose estimation after twelve hours of fasting with the spinal needle in situ. The patient was given 50 Gm. of glucose by mouth, and samples of spinal fluid were withdrawn for glucose estimation at one-half hour intervals for three hours. The blood specimens were also taken at one-half hour intervals. The resulting curves when plotted showed a slower ascent in spinal fluid glucose with no descent in three hours. The author suggests the adoption of a figure which he calls blood-spinal fluid ratio (the normal, 50:70) obtained by dividing the spinal fluid sugar percentage by the blood sugar percentage and multiplying the same by 100. In conclusion the author states that the spinal fluid sugars to be of any value should always be studied in conjunction with a simultaneous blood sugar estimation. The fasting level of glucose in the blood and spinal fluid in epidemic encephalitis is within normal limits.

POTTER, Akron, O.

SO-CALLED HERXHEIMER REACTIONS. KARL HERXHEIMER and HANS MARTIN, Arch. Dermat. & Syph. **13**:115 (Jan.) 1926.

The blurring of a previously clear-cut syphilitic eruption after antisyphilitic treatment is the usual manifestation of this reaction. Arsphenamine treatment is likely to cause a more severe reaction; and the reaction is likely to appear after a shorter period and to persist for a shorter time than is the case with mercury or bismuth treatment. This reaction is of diagnostic significance in those cases in which the exanthems are obscure clinically, in that the skin lesions may become acute after the administration of antisyphilitic medication. Intramuscular injection of 1 cc. of a 10 per cent oily suspension of insoluble mercury preparation, common bismuth salts or, best, silver arsphenamine injected intravenously in doses of from 0.15 to 0.2 Gm. is most suitable for specific provocative diagnosis of skin lesions. Such reactions associated with hyperemia and edema are not limited to the cutaneous surface of the body but may appear in every organ of the body. Depending on the intensity of the reaction and also the location of the lesions in a vitally important organ, antisyphilitic drugs may produce sudden changes which may endanger life. The symptoms noted, following antisyphilitic treatment, are signs of a hyperemic, edematous local reaction of the organs involved. The reaction described is that of an intermediate action between the specific organism and the hypersensitive cells of the patient. The final manifestation of this hypersensitive reaction is the development of hyperemia and edema in the tissues affected by syphilis. The nonspecific reactions which occasionally occur in nonsyphilitic skin diseases

may be due to the effect of antisyphilitic therapy, especially arsphenamine, on the protoplasm.

SCHUMACHER, Philadelphia.

EFFECT OF MENTAL AND EMOTIONAL STATES ON THE LEUKOCYTE COUNT. J. M. MORA, L. E. AMTMAN and S. J. HOFFMAN, J. A. M. A. **86**:945 (March 27) 1926.

No attempt having been made to study the leukocytic changes produced by mental and emotional states, the authors made a study of these changes in the peripheral blood of animals and man. Ten dogs were used and showed an increase of from 30 to 150 per cent in the leukocyte count when alterations in the emotional state were produced by placing a cat or a rat in a cage within plain view of a securely fastened dog and then applying external stimuli.

The second series of experiments was on thirteen patients presenting non-infected surgical conditions, the anticipation of the operation being used as an alterative of the mental and emotional states. Control counts were taken at frequent intervals during the second or third days previous to the operation and the final count was taken on the operating table just before the operation. In seven patients there was definite evidence of fear and apprehension, the other six being indifferent. The former showed an increase of from 12 to 100 per cent, while the latter presented little or no change—the increase in both dogs and man being in the polymorphonuclears.

The authors discuss briefly Muller's and Cannon's theory in explanation of this peripheral leukocytosis; they state that they have not attempted to demonstrate the mechanism of this phenomenon but emphasize that its practical import lies in the fact that it may frequently be the cause of a leukocytosis, particularly in operative cases, and that it may easily be confused with infective or other types of leukocytic change.

CHAMBERS, Syracuse, N. Y.

SPASMOPHILIA — INORGANIC CONSTITUENTS OF BLOOD AND CEREBROSPINAL FLUID. JOHN D. NOURSE, D. N. SMITH and J. D. HARTMAN, Am. J. Dis. Child. **30**:210 (Aug.) 1925.

Blood calcium is markedly reduced during the active stage of infantile tetany. The inorganic phosphorus content is either normal or elevated. The purpose of this work was to determine if a decrease in calcium content occurred in the cerebrospinal fluid in infantile tetany, if there was an increase in the inorganic phosphorus content, and if there was significant change in the other inorganic elements. The calcium content of brains in parathyroid tetany and infantile tetany has been found to be lower than in normal controls. There is also a change in the $\frac{Na + K}{Ca + Mg}$ ratio.

Inorganic phosphorus in the spinal fluid was increased in inflammatory diseases of the central nervous system, while sodium chloride was definitely lower than in normal cases. The average calcium content of the spinal fluid in cases of spasmophilia has been found to vary little from the normal. It is significant that the calcium of the blood serum is noticeably decreased during the active phase of spasmophilia, while the calcium content of the spinal fluid remains practically unchanged. In two cases of influenzal meningitis, the spinal fluid calcium was higher than normal, and in one of these the inorganic phosphorus was unusually high. The potassium content of the spinal fluid was greater than that in the blood.

WAGGONER, Philadelphia.

HYPERNEPHROMA OF THYROID, WITH CLINICAL PICTURE OF EXOPHTHALMIC GOITER. ANATOLE KOLODNY, Arch. Path. & Lab. Med. **1**:37 (Jan.) 1926.

The author reports the case of a woman who had had a goiter since the age of 15. At 68, she began to develop a typical picture of exophthalmic goiter, and on admission to the hospital, four months later, her basal metabolic rate was "plus 80." Bilateral subtotal lobectomy was performed, and the tissue removed showed multiple, circumscribed, opaque, yellowish white nodules, which, on microscopic examination, proved to be a typical reproduction of the cortical tissue of the suprarenal glands; a diagnosis was made of metastatic hypernephroma of the thyroid. Owing to the rarity of this condition, only one other case being found in the medical literature of the world, sections of the tumor were submitted to several prominent pathologists, who, with one exception, concurred in the diagnosis.

The author gives two possible interpretations for the occurrence of these nodules: one, that they were an overgrowth of aberrant suprarenal tissue in the thyroid, the other, that they were metastases from a hypernephroma. He considers the latter the more probable, because the former is found seldom in later life, and in all known cases of aberrant suprarenals the tissue was found below the diaphragm. Careful examination of the patient did not disclose the presence of a primary tumor.

PEARSON, Philadelphia.

BILATERAL CHARCOT HIP JOINTS. REPORT OF THREE CASES. JAMES L. GREENE and FRANCIS J. SCULLY, Am. J. Syph. **9**:704 (Oct.) 1925.

Roentgenograms in case 1 showed marked destructive changes of both hips. There was a definite history of syphilitic infection and the neurologic findings were typical of tabes dorsalis. Charcot joints develop most frequently in the ataxic stage of tabes dorsalis. In case 2, however, the patient developed the joint affection before the onset of the ataxia. Because of this, because it is often not recognized that many cases of bone and joint syphilis give negative blood Wassermann reactions, and hence recourse is not had to spinal fluid examination, and because the roentgenographic appearances are not distinctive, Charcot joints are not infrequently confused with tuberculous conditions. In case 3, the patient was only 14 years of age at the time of onset of the disease. This is a case of juvenile tabes from congenital syphilis. In October, 1919, the patient heard a cracking sound, in the right hip. Under the care of Dr. Dercum, roentgenograms were made showing a typical Charcot joint. In November, 1922, pain was felt in the left hip and roentgenograms showed a Charcot joint on that side as well.

SCHUMACHER, Philadelphia.

A MORPHOLOGIC STUDY OF THE FUNCTIONAL PSYCHOSES. FRANCIS C. SHAW, State Hosp. Quart. **10**:413 (May) 1925.

After the methods of Kretschmer, Viola and Naccarati the author proposes to show a relationship between the morphology and the psychoses. Fifty patients with manic-depressive psychoses and fifty with dementia praecox were selected for this study. To avoid any marked influence from difference in age, as many patients as possible under 30 years of age were used. A number of the manic depressive patients, however, were above this age. In the female group there was only one year of difference in the average ages of the two groups.

Comparing the morphologic index (ratio of the length of the limbs to the volume of the trunk) of these two groups, the dementia praecox group showed

an average higher index of 169.9 points in the males and 202.6 in the females. Compared with the normal morphologic index, the dementia praecox group was about 85 points higher and the manic depressive group about 85 points lower. The patients in the latter group averaged about 2/5 inch (1 cm.) taller than those in the dementia praecox group, but their limbs were 9 cm. shorter. There was an average difference in weight of 15 pounds (7 Kg.) in favor of the manic-depressive group.

HOWARD, Milwaukee.

ENURESIS AS A PSYCHOLOGICAL PROBLEM. HELEN T. WOOLLEY, Ment. Hyg. **10**:38 (Jan.) 1926.

Physical examination and the correction of defects found is the first step in the treatment of enuresis. Endocrine dysfunction may be a cause of enuresis. Since in as high as 90 per cent of the cases no physical cause can be uncovered it must, in these cases, be regarded as primarily a problem of habit training and the mental attitude of the child. Causes of failure in developing correct habits can be classified as follows: (1) postponing the period of training beyond the normal age — from 12 to 18 months; (2) establishment of the negative reaction — negativism; (3) love of emotional scenes — the child likes to be the center of interest; (4) fear — intense social disapproval is an even more common source of fear of not being able to control himself than severe physical punishment; (5) infantile dependence on the mother — the situation of being a baby is so satisfying to the child that he is loath to give it up; (6) relation to masturbation — this must always be borne in mind; (7) association with rudimentary feelings of sex — voiding of urine may come to have a primitive sexual value of its own. It is not held that any one situation alone may be displayed, or be present in pure culture, but one or another of them seems to be outstanding in these cases of enuresis.

SCHUMACHER, Philadelphia.

BISMUTH TREATMENT OF CEREBROSPINAL SYPHILIS. W. A. SMITH, and L. J. FOSTER, J. Nerv. & Ment. Dis. **62**:113 (Aug.) 1925.

The authors report treatment of twenty-seven unselected cases of cerebrospinal syphilis other than general paralysis and tabes for eighteen months, and find the following results: pains, numbness, paraesthesias, dizziness, headaches and urinary disorders were relieved. A case of syphilitic meningitis showed rapid recovery with no return of symptoms eleven months later. One case of spastic paraplegia was unchanged, while in the other six cases of spasticity the symptom was greatly diminished, especially in the gait. Five patients showing neurotic symptoms without signs of organic disease of the nervous system, but with positive blood Wassermann reaction, obtained marked relief. In two cases with positive blood Wassermann reaction, the tremor was improved in one and unchanged in the other. The use of bismuth did not reduce the Wassermann reaction with either blood or spinal fluid in cases of cerebrospinal syphilis. The authors believe, however, that treatment of the clinical symptoms is of greater importance than a negative serology. They state that bismuth is more effective in the treatment of subective than in the treatment of objective symptoms.

HART, Philadelphia.

UNILATERAL WRIST DROP DUE TO SYPHILIS WITH REPORT OF CASES. T. P. MURDOCK, Am. J. Syph. **9**:566 (July) 1925.

Syphilis as a causative factor of unilateral wrist drop is seldom, if ever, mentioned in the literature. Traumatism is generally accepted as the most common cause of unilateral wrist drop. In both cases reported here, paresthesia of the posterior aspect of the forearm and dorsal surface of the hand was noted. There was no history of lead poisoning, alcoholic debauch, chronic alcoholism or traumatism. The Wassermann reaction in both cases was 4 plus. In case 1, the onset of the wrist drop was sudden and without previous symptoms of neuritis. In case 2, for three days previously the patient had had some numbness in the forearm and hand; this patient left the city and was not seen again. The patient in case 1 was given six intravenous injections of sulpharsphenamine, 0.3 Gm. Following the third injection the condition improved, and it entirely cleared up after the sixth injection.

SCHUMACHER, Philadelphia.

THE EXCITABILITY OF THE ANEMIC MEDULLA OBLONGATA. F. ROBERTS, J. Physiol. **59**:460 (March 31) 1925.

Following a series of experiments on rabbits and cats, anesthetized with urethane supplemented by chloroform ether mixture, in which bulbar arteries were occluded and observations were made of blood pressure, corneal, swallowing and oculomotor reflexes, knee jerks, and the action of the respiratory center the author concludes that when the medulla is deprived of its blood supply for short intervals the pressor, depressor, corneal, oculomotor and swallowing reflexes, and knee jerks persist, while excitability of the respiratory center to afferent stimuli is suppressed.

POTTER, Akron, O.

MENINGOCOCCIC MASTOIDITIS. O. J. DIXON, Arch. Otolaryng. **3**:151 (Feb.) 1926.

A child was taken ill with earache. The drum was incised, and the tonsils and adenoids were removed while the child had an acute otitis. Four days later mastoid tenderness and rigidity of the neck developed and the case progressed to an acute mastoiditis with meningitic symptoms. At this point Dr. Dixon first saw the patient. Examination of the spinal fluid showed no bacteria, but an increase in the polymorphonuclear leukocytes. Operation showed necrotic mastoid cells with the dura in the middle fossa inflamed. Temporary improvement was followed by death. The necropsy and subsequent reports on the spinal fluid and blood cultures showed that this was a case of epidemic cerebrospinal meningitis with mastoiditis.

HUNTER, Philadelphia

TONIC SPASMS OF THE EYE MUSCLES IN EPIDEMIC ENCEPHALITIS. NINA POPOWA, Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:515 (July) 1925.

The author's conclusions, based on five cases of ocular spasm in postencephalitic parkinsonism, may be summarized as follows: attacks of tonic spasm of the eye muscles were observed; these spasms affected most commonly

the muscles which move the eyeballs upward, and less often those which move them downward or laterally; in a few cases the spasms were tonic, in others tonic-clonic, and in others they consisted of a series of short, rhythmic tonic spasms; the spasms ceased during sleep; the seat of the affection is in the corpus striatum; atropine and epinephrine shorten the spasms, and the effect of these drugs is in favor of the parasympathetic origin of the convulsions.

ALPERS, Philadelphia.

NARCOLEPSY OCCASIONALLY A POSTENCEPHALITIC SYNDROME. WILLIAM G. SPILLER, J. A. M. A. **86**:673 (March 6) 1926.

In this interesting statement Spiller gives a brief description of the condition called narcolepsy. He reports that cases were observed by Redlich and Perrier following encephalitis, or what they referred to as encephalitis, although in Perrier's cases nothing but the narcolepsy indicated a previous encephalitis. Spiller calls attention to the general belief that narcolepsy is extremely rare. He reports three cases that have come under his observation within a year; he believes that it would be assuming too much to assert that narcolepsy is always a postencephalitic syndrome, but that it would be well to recognize that it may be so. We should be on the alert to detect it, especially since Redlich holds out hope for recovery.

CHAMBERS, Syracuse, N. Y.

POSTINFECTIOUS AND ISOLATED PARALYSIS OF THE SERRATUS MAGNUS. MAGNUS A. TOURNAY and W. M. KRAUS, J. Neurol. & Psychopath. **5**:115 (Aug.) 1924.

Isolated paralysis of the serratus magnus muscle is extremely rare. The occurrence of this lesion following an attack of influenza is even more uncommon. The authors found only three such cases in the literature. They present three new cases and give in careful detail all the postive and negative signs and symptoms needed to establish the diagnosis. They conclude that, in pathogenesis, no one factor alone is responsible. Carrying heavy weights, plus the presence of a rudimentary cervical rib, probably suffices to cause the paralysis. When infection is added it presumably produces the paralysis by striking a "locus minoris resistentiae."

FAVILL, Chicago.

A CASE OF DIFFUSE SCLERODERMA PRESENTING UNUSUAL FEATURES. CHARLES M. WILLIAMS, Arch. Dermat. & Syph. **9**:187 (Feb.) 1924.

A detailed account is presented of scleroderma, in a child, aged 7, which showed continuous progress for five years. The neurologic findings of dissociation of deep reflexes and hyperesthesia, and the distribution of the skin lesions point tentatively to a localization of the disease in the dorsal root ganglia of certain levels. It is merely suggestive that the cause of this nervous disease may be some toxic irritant, with or without an associated endocrine dysfunction.

ANDERSON, Philadelphia.

BLOOD CALCIUM IN SPASMOPHILIA. J. P. CROZER GRIFFITH, J. A. M. A. **86**:828 (March 20) 1926.

The degree of blood calcium content with two brief case histories and the age limits of spasmophilia are discussed by the author. He reports the case of an infant, aged 5 weeks, presenting spasmophilia manifestations and believes that spasmophilic symptoms may manifest themselves even in the early weeks of life.

CHAMBERS, Syracuse, N. Y.

Society Transactions

BOSTON SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, Feb. 18, 1926

DONALD GREGG, M.D., *President, in the Chair*

VASCULAR LESIONS IN A CASE OF CHRONIC ENCEPHALITIS LETHARGICA WITH PARKINSON'S SYNDROME. DR. STANLEY COBB.

This is a case studied in the laboratory of Professor Lhermitte in Paris. The patient was a chauffeur, aged 42, who four and a half years before death had fever and diplopia. These symptoms lasted a few weeks, and there gradually

Left motor cortex; dilated blood vessels with areas of hemorrhage.

developed a rigidity which interfered considerably with his walking and eating. Little by little he became more and more helpless until finally, when he was committed to the Paul Brousse Hospital, he was a perfect picture of Parkinson's syndrome, with rigidity, tremor and movement of the trunk and limbs en bloc; he also showed some interesting sympathetic symptoms: ruddy face, marked seborrhea and conspicuous increase of salivary secretion. Three years after the onset of the disease he became completely bed-ridden and lay rigid without spontaneous movement. He died four and a half years after the onset.

Postmortem examination showed unusual vascular changes which may be summarized as follows:

Cortex.—Marked vascular changes throughout, with increase in number and size of vessels. Great congestion; vessel walls either thin or thickened, hyaline and sclerotic. Hemorrhages in the white matter of both motor areas, with iron deposit in hemorrhages and about nearby vessels. Adjacent cellular destruction ascribable to ischemia; also chronic inflammatory changes in frontal and parietal cortex not immediately affected by hemorrhages; slight leptomeningitis; slight marginal gliosis; marked perivascular gliosis. "Mucin-like" bodies in cortex; abundant "amyloid" bodies and intermediate stages.

Basal Ganglia.—On right and left marked chronic cellular degeneration is found throughout, especially of the pallidal cells; more acute changes in putamen, necrotic areas near sclerotic blood vessels, especially in the pallidum. Abundant amyloid bodies. Numerous and congested blood vessels, some with thickened and hyaline walls, some thrombosed vessels, others contracted and empty. No hemorrhages. Rings of iron deposited in adventitia of vessel walls of part of the right pallidum. Perivascular and diffuse gliosis. The most interesting study in these specimens is that of the sections colored with Pearl's iron stain. In the pallidum are found many blood vessels with dark blue rings of iron in the vessel walls. These are for the most part the vessels mentioned as having hyaline walls, but a study of the distribution of these iron-ringed vessels shows that they are restricted to the pallidum and for the most part to the inner segment. The hyaline-walled vessels, on the other hand, are found throughout the rhombencephalon and to a less extent in all parts of the brain. A close inspection of these iron-ringed vessels shows that the ferruginous deposit lies in the adventitial layer of the vessel wall, and largely in the newly added adventitia — the thickening of the vessel resulting from inflammation in the perivascular space. In some cases the iron ring is narrow and lies in a thin layer of connective tissue. In other cases, in which the Virchow-Robin space is distended with organized exudate, the iron makes a broad band. Many vessels have hyaline degeneration outside of the thickened adventitia. It is thus seen that the iron lies in the connective tissue beneath the hyaline and outside the media of the vessel wall.

Midbrain.—Bilateral depigmentation and degeneration of locus niger. Extensive vascular lesions like those described in the basal ganglia. Cellular destruction in the left third nucleus. Chronic ependymitis.

Cerebellum.—Degeneration of cells in the dentate nucleus, subacute and chronic vascular lesions nearby, surrounded by necrosis. Myelin degeneration in the superior peduncles. Vascular lesions in the pontile tracts and nuclei, and in one inferior peduncle.

Medulla Oblongata.—Perivascular lymphocytosis in somewhat patent Virchow-Robin spaces. Chronic sclerotic changes in the vessel walls with surrounding necrosis of tissue, especially near the inferior olivary nuclei.

Spinal Cord.—Diffuse peripheral myelin degeneration. Thick-walled blood vessels with some perivascular infiltration. Chronic leptomeningitis.

Dorsal Roots and Ganglia.—Chronic pericellular fibrosis.

Muscle.—Chronic atrophy and fibrosis.

Skin.—Local hypertrophy of sebaceous glands.

Comment.—The case is interesting for several reasons. In the first place it has these unusual vascular dilatations in the cortex and adjacent white matter which caused hemorrhages and perhaps death. Also the finding of iron deposits in the adventitial spaces of these vessels may indicate that iron, as a product of

degeneration, is carried to vessel walls in the pallidum. This deposit of iron in the vessel walls, however, is apparently so common that one should look on it as normal (Hurst, E. W.: *J. Path. & Bact.* **29**:65 [Jan.] 1926) and relative to the high iron content of the globus pallidus. The sclerotic and hyaline changes in the vessel walls are distinctly abnormal; the cell destruction is marked; there is lack of pigment in the substantia nigra; all typical pathologic findings in "post-encephalitic parkinsonism." Cases such as these make us realize what a chronic course epidemic encephalitis may run, and what great damage to blood vessels occurs. How often this may eventually lead to cerebral hemorrhage remains to be seen, but I may venture to predict that many recovered cases of epidemic encephalitis will have vascular accidents at an early age.

DISCUSSION

DR. D. J. MACPHERSON: There are three striking things about the pathologic changes in encephalitis leading to the parkinsonian syndrome. First, there are always multiple lesions; second, both chronic and acute lesions occur at the same time. This is of particular importance because the virus is of the type that may lie dormant in the nervous system for a long period of time. In London they are beginning to see cases first showing onset of parkinsonian syndrome five years after the original attack of encephalitis. Third, there are almost constant lesions in the substantia nigra. Whether this lesion is essential for the parkinsonian state is a question, because it is always associated with other lesions. It would seem more probable that we are dealing with an injury to the extrapyramidal system, and that a lesion either in the globus pallidus or its projection system may produce the symptomatology. It does seem, however, that the globus pallidus is peculiarly susceptible to the virus of encephalitis.

DR. E. W. TAYLOR: Is there any special lesion in the lenticular nucleus? Or do you attribute the symptoms to lesions lower down?

DR. COBB: I am not sure. We have had lesions in the pallidum, and these iron rings were in that region only. They often arise there in normal persons and with various inflammations; so they are not especially specific. The unusual condition is the hemorrhages. I should be interested to know if any one else has had experience with such small multiple hemorrhages.

DR. H. R. VIETS: One question about the cause of death of encephalitis patients. They die of hemorrhage of the brain, but they do not die, in my experience, an apoplectic death. They have small multiple hemorrhages scattered diffusely throughout the brain, not a single ruptured vessel. We have recently seen a case of three years' duration with typical onset, followed by a long period of slight but definite lethargic attacks, with death within a week from an ascending paralysis, not apoplectic in type. At necropsy small hemorrhages were found in both the medulla oblongata and the brain. Do any patients with encephalitis die an apoplectic death?

DR. COBB: They are almost all small scattered hemorrhages.

DR. MACPHERSON: It is interesting to note the apoplectic form of hemorrhage in this disease. Collier reported four cases in which the illness was initiated by a stroke (so called), and it was evident from the symptomatology which developed that the disease was epidemic encephalitis.

DR. DONALD GREGG: Is there any way to tell when the encephalitic process is completely ended? A normal spinal fluid finding seems to show at least a quiescent or dormant period. Am I correct in inferring that even when a

normal fluid is found it is to be expected that the process will probably continue, although there may seem to be a temporary remission?

DR. COBB: The only answer I can make is that this patient had subacute inflammation in the hind brain and chronic scars elsewhere. He had been sick about four and a half years; he had lesions in all stages. The infection was evidently active in a mild way over all those years. There was nothing reported in the spinal fluid.

THE EFFECT OF CONSTITUTIONAL FACTORS IN INFLAMMATORY REACTIONS IN THE NERVOUS SYSTEM. DR. D. J. MACPHERSON.

In investigating the variables that influence cellular reaction in the nervous system, I have made an attempt to study the effect of altering the environment (in the sense of body fluids and hormones) in the presence of a constant stimulus. Guinea-pigs and rats were the animals used, and an incision into the cortex of the brain under aseptic precautions was the lesion studied. All animals were killed by ether nine days after operation. Four series were studied: normal adults, animals receiving aqua amygdalarum amararum, animals receiving phenylhydrazin and rats from which the thyroid gland was removed by cautery.

In the study of the serial sections, the normal animals showed a marked proliferation of the connective tissue growing deep into the incision. There was also proliferation of the connective tissue cells from the neighboring blood vessels. On the margin of the incision were large numbers of cells of the lymphocytic series and a few gitter cells. There was some swelling of the ganglion cells in the neighborhood of the lesion, with numerous trabant cells, increase in the glial nuclei in the surrounding tissue, and some indication of a beginning increase in glial fibrils.

In the animals treated with aqua amygdalarum amararum, the proliferation of the pia and ingrowth of the connective tissue cells in the incision was much less marked than in the normal. There were almost no cells of the lymphocytic series present. There was a more severe and extensive degeneration of ganglion cells; but instead of the trabant cells and increase of the glial nuclei, numerous giant glial cells of the ameboid type were found in the intervening tissues.

In the animals treated with phenylhydrazin, there was an excessive proliferation of connective tissue exceeding the normal. A moderate number of lymphocytes were present. Again there was marked degeneration of ganglion cells, but almost no glial reaction, and only a rare ameboid form. An interesting associated finding in these animals was a marked internal hydrocephalus. The control brains in the phenylhydrazin series showed marked hyperemia, with an occasional petechial hemorrhage, but no lymphocytic reaction.

Of the rats developing myxedema, only one survived the operation. This animal showed a marked pial proliferation with but little ingrowth into the incision. There were more gitter cells present and slight lymphocytic reaction, severe degeneration of the ganglion cells and only slight reaction of the glia.

The indications from this series of experiments were that connective tissue is the most resistant tissue present in the nervous system; the failure of the glial reaction varied in the other series, the most severe toxic action apparently taking place in the animals treated with aqua amygdalarum amararum. Whether these reactions were due to diminished oxygen in the blood in the one case, to anemia in the second, to the myxedematous condition in the third or to a direct toxic action on the tissue itself, it is impossible to determine by

these experiments. It is to be noted, however, that the constitutional factors played a marked rôle in the pathologic picture as presented to the microscope.

DISCUSSION

DR. E. W. TAYLOR: Can you draw any general conclusions as to inflammation?

DR. MACPHERSON: I think it is very difficult, in such a small series, to draw any general conclusions. It was more of an orienting study. We were merely trying to find out if it was possible to influence the cellular reaction by factors other than those due to the disease itself. Apparently that is possible. The chief point is that the connective tissue is much more resistant than the glia, and that the lymphocytic picture varies very widely in the series studied.

ON THE NATURE OF THE CEREBROSPINAL FLUID.* DR. FRANK FREMONT-SMITH.

My purpose is to review the important evidence regarding the points of origin and absorption, and the mechanism of absorption of the cerebrospinal fluid. It may be accepted as established that the choroid plexus is the chief source of the cerebrospinal fluid, and that absorption takes place chiefly through the arachnoid villi into the venous sinuses. There is also good evidence that the mechanism of absorption is determined by the relative hydrostatic and osmotic pressures of the cerebrospinal fluid and the blood in the dural sinuses. The direct evidence for the secretion theory rests on morphologic cell changes in the choroid plexus. These changes are exactly opposite to those seen in actively secreting glands. The cell changes regularly accompany any increase in the formation of fluid and may be regarded as evidence of such increased formation. They in no way indicate active secretion and are as readily interpreted as evidence for dialysis.

The cerebrospinal fluid pressure is normally higher than the cerebral venous pressure, and varies directly with the capillary pressure in the choroid plexus, excepting when the osmotic pressure of the plasma is changed. If this osmotic pressure is diminished the spinal fluid pressure increases, while if the plasma is made hypertonic the fluid pressure will fall, and the flow through the choroid plexus appears to be reversed. The analogy between cerebrospinal fluid and the aqueous humor of the eye is significant.

In comparing the chemical contents of the plasma and cerebrospinal fluid, the striking contrast lies in the protein, which is almost absent from the cerebrospinal fluid, and the chlorides which are present in much higher concentration in the cerebrospinal fluid than in the plasma. Mestrezat showed that the osmotic pressures of the plasma and cerebrospinal fluid are identical. The experiments in which he reproduced cerebrospinal fluid by dialysis from plasma and also from the peritoneal cavity are important.

My results, in collaboration with Miss M. E. Dailey, show that a relationship exists between the concentration of protein in the plasma and the distribution of chlorides between plasma and cerebrospinal fluid—analogous to the equilibrium between plasma and pleural or ascitic fluids described by Loeb, Achtley and Palmer, and to that between plasma and red blood cells, studied by Van Slyke, Wu and McLean. The Donnan membrane-equilibrium appears to play a significant rôle in these relationships. The similarity, in

* From the Neurological Laboratory, Massachusetts General Hospital, and the Department of Neuropathology, Harvard Medical School.

chemical composition, of the cerebrospinal fluid to the glomerular filtrate of the frog, recently described by Wearn and Richards, is significant. An analogy is suggested between the cerebrospinal fluid and that protein-free fluid which, in many parts of the body, is believed to be continuously filtered from the arterial side of the capillaries into the tissue spaces and reabsorbed by the venous side. An explanation may be offered for the development of internal hydrocephalus on the basis of hydrostatic and osmotic pressures.

It is concluded that there is no good evidence for the secretion of cerebrospinal fluid; that the evidence, taken as a whole, is overwhelmingly in favor of dialysis; and that the laws which determine the simple membrane-equilibrium existing between plasma and cerebrospinal fluid have fundamental significance for the mechanism of fluid exchange in the organism.

DISCUSSION

DR. L. J. HENDERSON: This paper seems to be entirely satisfactory. The results, no doubt, will be modified in time because they will have to be extended and because the theories of physical chemistry are likely to change; but I have no criticism whatever to present on the conclusions that have been reached. It seems to me they afford sound and promising working hypotheses, and in the main they are likely to stand as the true interpretation of the phenomena.

Evidently it is out of the question for me to undertake to discuss the neurologic problems. Perhaps it would be interesting for me to say a word about this type of physical chemistry and its bearing on medicine. The reason why these things are interesting, fundamentally interesting, is because beneath the structures of the histologists there are the physicochemical structures. The processes which go on in these are the very foundation of all organic activity. First of all, the body is made of water, not pure water, but water containing a collection of salts, acids and bases, and then the proteins. If we had perfect understanding of all the physicochemical relations and interrelations between these things, we should be going far toward a thorough foundation of general physiology. The reason is that here, as in the field where the engineer works, a description is also an interpretation of things. When you understand the structure of the physicochemical system you understand the function of it. Here where you have a clear interpretation of what things are you see the relations and you see how they work. Not only is that true, but it is also true that as you pass in the direction in which Dr. Fremont-Smith has been going you come to understand the relations between the physicochemical phenomena and the phenomena that deal with slightly larger structures, and so you make the connection between physicochemical phenomena and the other better known phenomena on a larger scale; and in time the circulation in general, the properties of blood pressure, etc., are seen in their organic unity.

In the process that takes place in the formation of the cerebrospinal fluid, dialysis is evidently of first importance. It would be unreasonable to suppose that the organism goes to the trouble to construct this apparatus and that it then does things in a roundabout way that can take place spontaneously. It may be that there are slight modifications of the simple physical phenomenon which may arise because of peculiarities of the membrane.

We are now on the verge of a development in physiology involving the properties of blood, the laws of the circulation and the laws of diffusion, which is destined to go beyond a mere physical or chemical or physicochemical analysis. Claude Bernard saw that such is the task of physiology, but he

was not understood in his day and few have understood him since. It will soon be possible for us to see the interconnections between more and more of the phenomena that have been studied as separate phenomena, as belonging to chapters of physiology. You have had an illustration tonight that in order to understand the formation of cerebrospinal fluid it is necessary to have a clear appreciation of the nature of blood, of dialysis and of a great many other processes. The facts have been reduced to quantitative formulation. However difficult it may be to understand for the first time such units, once learned they will afford an enormous saving of labor.

DR. J. C. WHITEHORN: Have you encountered any spinal fluid chlorides considerably higher than the normal range? If so, what were the plasma proteins? Secondly, the interpretation of the effect of protein as analogous to a Donnan equilibrium suggests that the albumin of the plasma may be of greater importance than the globulin. Is there any evidence indicating such a difference in effect on the chlorides of the cerebrospinal fluid?

DR. FREMONT-SMITH: We have had few cases with spinal fluid chlorides higher than 750 mg. per hundred cubic centimeters. In these the plasma chlorides were also elevated, while the plasma proteins were within normal limits. We have had no case with plasma proteins much above 8 per cent. Theoretical considerations would lead us to expect a greater "Donnan effect" from the albumin than the globulin of the plasma, as Dr. Whitehorn suggests. We have not sufficient data as yet to draw conclusions in regard to this point.

DR. J. B. AYER: Dr. Fremont-Smith has said that this work was carried out in my laboratory. I wish you could compare the work of the old laboratory with that of the new one under his direction; the studies in the old one were largely macroscopic and microscopic; the present work is largely that of quantitative chemistry. The problems Dr. Fremont-Smith has set himself are fundamental in character, from both physiologic and pathologic points of view. While most of his results are as yet intangible from the practical side, the imagination readily sees in this work the explanation of certain headaches and the mechanism of certain types of hydrocephalus. Other problems dependent on disordered fluid-blood balance are unquestionably waiting just around the corner. It is interesting to note how this work is drawing neurology back to general medicine, and the recognition that the elucidation of problems of structural neurology is through the same channels as other forms of medicine.

I wish to thank Dr. Fremont-Smith for his clearcut exposition of the problem of blood and fluid chemical interchanges. Dr. Henderson assures us that his conceptions are sound. I myself have no intelligent judgment in the matter, but shall offer every encouragement for the continuation of the work.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 18, 1926

JOHN FAVILL, M.D., *Vice President, in the Chair*

PSEUDOTUMOR SPINALIS. DR. ROY GRINKER.

The conception of pseudotumor spinalis, originated by Nonne, was based on four cases diagnosed clinically as cord tumors which recovered completely with indifferent therapy. It was considered that the tumors had regressed. Oppenheim believed that pseudotumors were cases of chronic myelitis, neuritis

of the cauda roots, small tumors overlooked at operation or microscopic tumors. Elsberg and Kennedy reported five cases of supposed tumor which turned out to be lumbosacral neuritis. Chronic arachnoperineuritis, usually a primary meningeal disease, although at times secondary to vertebral or cord disease, may cause tumor symptoms, especially if associated with fluid accumulation. Nonne reported one case with tumor symptoms after trauma in which no pathologic change was found by Wohlwill.

A colored laborer, aged 35, had had mild pain in the back for eighteen months, severe for three weeks. Lately he had had difficulty in walking and the day before he was seen excrutiating pain developed in the legs which suddenly disappeared leaving the legs completely paralyzed and without feeling. The essential findings were an almost complete flaccid paraplegia with coarse fibrillations in the thigh muscles and no atrophy. Sensation of all types was lost below the level of the third lumbar root. The Achilles, cremasteric and rectal reflexes were absent and the plantar response was flexion. There was double incontinence. Spinal puncture revealed the complete syndrome of Froin with 32 cells. Roentgenograms and all laboratory tests gave negative results. Four days later the patient had three generalized convulsions and died.

Necropsy revealed marked hyperemia and edema of the lungs. The brain and its coverings were normal; the spinal fluid was uniformly yellow, and no tumor was visible in the cord. Histologically, the axis cylinders of the cord and roots were moderately swollen and tortuous. There was no glial reaction or increase in lipoids. The myelin sheaths were normal. The ganglion cells of the lumbosacral cord revealed central chromatolysis, and many were degenerated and undergoing neuronophagia. The pia was normal. The arachnoid and perineurium were thickened with collagenous connective tissue which had a meshlike structure. Within the meshes was considerable connective tissue debris, much old blood pigment, crenated red cells and amorphous material. The vessels were dilated and many were ruptured. There was a moderate number of large round cells in the arachnoid.

The essential pathologic condition is considered to be a chronic arachnoperineuritis giving rise to the syndrome of Froin. Only early retrograde changes were seen in the roots and cord. The recently developed paralysis is possibly explained by a localized accumulation of fluid, suggested by the distention of the meshlike arachnoid; this may have served as a functional block to the roots. The cause of death may well have been the rupture of a delicate arachnoidal adhesion resulting in a sudden intermingling of a highly albuminous fluid with the normal, and a disturbance in the fluid equilibrium which also resulted in the genesis of convulsions.

Pseudotumor is not an entity. Either a tumor is present or another disease can be found. When organic symptoms are present a pathologic change can be found. Cases reported with pathologic changes supposedly too mild to cause the symptoms present are to be considered as an improper evaluation of the findings.

DISCUSSION

DR. G. B. HASSIN: Were you present at the postmortem examination and was a collection of spinal fluid present?

DR. GRINKER: No, there was not.

DR. HASSIN: The discrepancy in Dr. Grinker's case between the pathologic changes shown and the clinical picture is rather striking. It was also great in a case published by Dr. Favill and myself (*J. Nerv. & Ment. Dis.*, July, 1925).

A colored woman, aged 54, was admitted to Cook County Hospital complaining of pain in the chest, weakness in the legs and numbness below the nipple line. The legs were spastic, the tendon reflexes were exaggerated, Babinski and Gordon signs were positive; sensory disturbances were found below the nipple line and there were also bladder disturbances. The sternum protruded markedly because of a retrosternal tumor and the patient had had hysterectomy performed some years previously. At the necropsy a carcinomatous invasion of the second and third dorsal vertebrae was found with a mild peridural infiltration (lymphocytes and plasma cells) and hyperplasia of the epineurium of the posterior roots. No structural spinal cord changes were found that could be held responsible for the clinical picture, which was that of a dorsal myelitis. Probably this case also might be classified as pseudotumor spinalis. It is rather remarkable that the latter usually occurs in the lower segments of the spinal cord and especially in the region of the cauda equina. However, the majority of reports of such cases are without histopathologic studies such as presented by Dr. Grinker in his case.

DR. GRINKER: No accumulation of fluid was found at necropsy, but in removing the cord when one expects to find a tumor it is quite possible that something was destroyed. Certainly it would have been worth while to have studied the cord and meninges by serial sections when possibly a broken up adhesion might have been found. With nothing else present than the mild findings described, I think we must explain the syndrome on those findings. I believe we must give more weight to such mild findings in explanation of symptoms, rather than state that the pathologic changes are not sufficient to account for the clinical picture.

FACIAL DIPLEGIA IN MULTIPLE NEURITIS. DR. ALBERT B. YUDELSON.

Facial diplegia as part of an ascending, acute, infectious polyneuritis has been reported by Gordon Holmes and by Rose Bradford among troops at the front during the World War. An anaerobic streptococcus was isolated from the cord and brain in fatal cases of Bradford's series by Wilson. The following case, observed at the Wesley Memorial Hospital, is an example of infectious polyneuritis and illustrates the variability in the mode of onset. The patient, a woman, aged 45, had a mild attack of influenza in January, 1925, from which she recovered in a few days. On a day in the latter part of February she became chilled through; that night she developed diarrhea with some fever which lasted a few days and recurred at intervals for a month during which she lost 15 pounds (7 Kg.) in weight. She then improved and by the middle of May had regained the lost weight and felt well. While housecleaning at this date she experienced pain in the legs which was worse at night. Late in May a chilly sensation appeared in the feet and they felt numb for a few days; the gait also became weak and uncertain. Weakness of the legs continued and in the middle of June severe pain appeared in the hips, legs and feet and the patient became unable to walk. About the end of June the right side of the face was drawn up and the left corner of the mouth drooped; a few days later the right side of the mouth also drooped and the face became symmetrical; the patient could not close the mouth or eyes completely, could not speak plainly and could not move the lips at all. Deglutition was not involved.

When examined at the hospital, July 22, 1925, there was complete bilateral facial paralysis. No other cranial nerve was involved. There was no palsy of the neck, shoulders or arms. All movements of the legs were slow and weak,

especially those involving the flexors. There was some ataxy in the heel-to-knee test and some impairment of tactile sensibility. The plantar reflexes and the knee and ankle jerks were absent on both sides. The abdominal reflexes were present and the tendon jerks in the upper extremities were present but subdued. One week after entering the hospital the patient complained much of paresthesia without pain in the fingers and of severe pain and tenderness in the legs.

At first the facial muscles did not react to faradism or to galvanism, but on the thirteenth day galvanic excitability was present. All laboratory examinations gave negative findings; lumbar puncture was refused.

Improvement began soon after admission to the hospital and recovery is now almost complete, the tendon jerks in the lower extremities having returned. The lips, however, are still somewhat weak and the patient is unable to puff out her cheeks; there is difficulty also in pronouncing labials.

DISCUSSION

Dr. Lewis J. Pollock: I would like to know how many cases Dr. Yudelson found in the literature. In 1916 Patrick found twenty-nine cases in the literature in addition to eleven which had been previously reported.

The striking thing to me is that Bradford and Holmes observed many more cases in the World War than Patrick was able to find in the whole medical literature up to 1916. The fact is that they were dealing with a disease which was not multiple neuritis. This is brought out by the work of Foster Kennedy who, I think, supplies an apt name in "infective neuronitis." It is known that the cases we call peripheral neuritis have changes in the central nervous system, especially in the diphtheritic, diabetic and lead forms. If we considered them all neuronitis and classified them as such our understanding of the disease would be much clarified. I think it was Osler who first described an infective polyneuritis. Although Dr. Yudelson's case began with fever I do not think that means that it was an infective neuronitis, and therefore the context of his paper is not applicable to his case. If it was an infective neuronitis the title of his paper is inaccurate.

Dr. Meyer Solomon: I should like to know whether there was any tendency for this patient to have the normal emotions of fear, joy and so on.

Dr. Yudelson: There was no mental change in our case. The woman was quite emotional when she looked in the mirror but otherwise there was no mental instability.

Dr. Solomon: I asked that question because of the value of cases like this in solving the problem of the mechanism of the emotions. The peripheral or James-Lange-Sergi theory maintains that the peripheral (skeletal and visceral) changes are responsible for the subjective state. In extensive multiple neuritis with facial diplegia and widespread sensory and motor loss, if the mind is clear and if the patient can experience emotional feelings even though their expression is more or less cut off, it is some evidence in opposition to the peripheral origin of emotional feeling, so far as the skeletal system is concerned at any rate. In Dr. Yudelson's case, in spite of the facial diplegia, the paralysis was not very extensive and the sensory loss was slight.

Dr. Peter Bassoe: When I read the title of Dr. Yudelson's paper I wondered why he and others before him have singled out the facial nerve for attention in connection with multiple neuritis. To be sure, its involvement is conspicuous, but I hardly think it is of greater significance than the involve-

ment or not of other nerves. I think the smallness of the number of reported cases is explained by the fact that a great many observers have not realized that this particular involvement was worthy of record.

Dr. Yudelson: I believe I can answer the discussion of both Dr. Pollock and Dr. Bassoe by stating that it was not intended to say that facial diplegia is a rare thing, but rather to bring out the thought that in febrile multiple neuritis the facial pair is apt to be involved as often or oftener than any other set of nerves.

As to the question of neuronitis, Gordon Holmes differentiated his cases from every known form of peripheral neuritis as well as from disease of the central nervous system. Bradford, in summing up his cases, stated: "So-called acute febrile polyneuritis is a very definite entity, capable of being separated clinically from other diseases of the nervous system." He differentiated his cases from peripheral neuritis due to organic or metallic poisons. This paper presents the idea that bilateral facial palsy is not rare but rather common in febrile polyneuritis.

Replying to Dr. Solomon, I was unable to find out whether the patient's emotional reaction was due to extreme pain or because of the facial deformity. It seemed that the pain increased emotionalism because she cried most when she was covered with a blanket, the pain distressing her greatly.

Treatment of Neurosyphilis with Tryparsamide. Drs. D. E. Singleton and Jacob Paskind (by invitation), and Dr. Clarence A. Neymann.

Fifty cases of neurosyphilis treated at the Edward Hines, Jr., Hospital make the basis of this report. They include eighteen cases of general paralysis, twelve of taboparalysis, four of tabes and sixteen of cerebrospinal syphilis (ten endarteritic, three meningitic and three primary optic atrophy). Of the eighteen patients with general paralysis, five made a social recovery and were discharged; four showed improvement; nine were unimproved. The five recovered cases showed negative serology. Of the twelve patients with taboparalysis, four made complete social recovery; two were greatly improved; six were unimproved. Three of the socially recovered cases showed completely negative serology. Of the four tabetic cases treated, two showed improvement and two remained stationary; however, the serology improved after tryparsamide treatment in all four cases. Of the sixteen cases of cerebrospinal syphilis, three made social recovery; four showed improvement; six showed very little, if any, improvement. Two of the cases of primary optic atrophy showed serologic improvement; one was unimproved. The vision in these cases remained unchanged. Five per cent of the cases showed a slight transitory toxic amblyopia. Three cases showed a permanent but not marked reduction of vision. Eye examinations were made weekly after each treatment. Social recovery was seen in 50 per cent of all cases. The advanced deteriorated types showed no improvement. The parenchymatous type responded more favorably to tryparsamide than the mesoplastic type. Eye complications in properly controlled cases are considered to be practically negligible. The drug is easily given and no toxic after effects are noted.

DISCUSSION

Dr. William H. Holmes: The literature on the treatment of syphilis of the central nervous system contains many references to the importance of watching the effect on the eyes, but little is said about the effects of treatment on other viscera. This presentation deals with the effects of treatment

of fifty cases of syphilis of the nervous system. I would like to ask whether the clinical evidence of syphilis in these cases was exclusively nervous or whether there was syphilitic involvement of other viscera. In what proportion was aortitis found and what was the effect of treatment?

DR. MEYER SOLOMON: I would like to know whether the authors would be favorable to the idea expressed by Solomon and Viets of giving weekly treatments up to from fifty to seventy-five doses.

DR. NEYMANN: In some of the cases reported there has been transitory trouble with vision but it has disappeared quickly and there has been nothing approaching blindness. As to the question of vascular syphilis of the central nervous system, we admit that when we have a patient showing the mental and laboratory findings of general paralysis we classify the case as such. It is probably true that some of the cases reported by us as general paralysis were really the milder forms.

I think we have proved in this paper that optic atrophy is not a contraindication to giving tryparsamide. Some six years ago I read a paper before this society on the treatment of syphilis of the central nervous system with arsphenamine and neoarsphenamine, given intravenously and according to the Swift-Ellis method. In those cases we got about 25 per cent good results. With tryparsamide we have obtained about 50 per cent good results. I do not know whether the cases will relapse, but we have classified none of these patients as recovered until they were able to maintain themselves in the outside world without difficulty for several months. These patients are working.

DR. PASKIND: Of course tryparsamide will not cure every case of neurosyphilis, but tryparsamide has shown us improvement in many cases that nothing else had touched. We do not discharge these patients until six months after every sign of disease has disappeared. If they do not report regularly we go out after them. One patient who received about fifty injections of tryparsamide has been out for a year. He has made a social recovery, has gone back to his prewar occupation and is getting along. We have so far not had a patient come back after having been discharged as having made a social recovery. In several cases that started to show eye changes the symptoms quickly cleared up. At first, as soon as any eye changes appeared we stopped treatment, but we do not do that now. Often the eye changes improve between two courses of treatment.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 26, 1926

WILLIAM G. SPILLER, M.D., *President, in the Chair*

TUMOR OF THE THIRD VENTRICLE WITH UNUSUAL CLINICAL SYMPTOMS. DR. ETHEL C. RUSSELL.

The chief interest in this case is that while the symptoms were those commonly attributed to hypophysial dysfunction, neither operation nor necropsy revealed a pituitary tumor. In the past few years, Camus and Roussy have suggested that many of the phenomena associated with hypopituitarism may be due to lesions of the tuber cinereum and surrounding structures. This is still a fertile field for investigation, with as yet no definite conclusions.

A housewife, aged 50, admitted to the neurosurgical service Dec. 4, 1924, eight months previously had first noted dimness of vision, when, as she expressed it, "There seemed to be a cloud before my eyes." She had continued to lose vision and for six months she had been able to read only the large headlines in the newspaper. Four months previously she had visual hallucinations of black dogs. She drank about two quarts of water daily and was very fond of sweets. She complained of nervousness, of occasional bitemporal headache and less frequently of occipital pain. She was sleepy all the time and tired easily. The menses had ceased six months before admission, and she had had amenorrhea for one year previous to that time. Several years ago, she had one miscarriage at nine weeks and no other pregnancies. There was nothing of interest in the previous medical history except that she had had whooping cough at the age of 47. The family history was unknown to the patient.

Examination.—The patient weighed 243 pounds (110 Kg.), having gained 50 pounds (23 Kg.) in the last seven months. The basal metabolism rate was minus 21. The roentgen ray showed no enlargement of the pituitary fossa, the measurements being 10.5 by 7.5 cm. The vision was: right, 6/22; left, 6/15. The pupils were sluggish to light and the fundus showed a grayish yellow. The Bárány report was that of a cerebral lesion. The serologic examination gave negative results, the intraspinal pressure being 18 mm. of mercury. As there were no field defects, operation did not seem justified and the patient was placed on glandular feeding. Six weeks later, her physician reported that a left homonymous hemianopia had developed. She returned to the hospital and because of the endocrine disturbances, together with the visual field defects, a tentative diagnosis of suprasellar lesion was made and a transfrontal operation was done. The chiasm was exposed and nothing suggestive of a tumor was seen for 1 cm. between the surface of the chiasm and the diaphragm over the pituitary. Following this operation, the headache persisted and the vision was rapidly being lost; accordingly a right subtemporal exploration and decompression was done.

The patient was discharged, Feb. 25, 1925, considerably relieved of headache. Six months later the visual fields had enlarged considerably. However, she was restless, had headache and drank four quarts of milk daily. Her appetite was enormous and she was difficult to manage, having become childish and irritable. She was uncleanly in her personal habits and incontinent. She had delusions; at one time when she was brought in for examination she insisted that she had come with a horse. Her mental deterioration continued until Jan. 10, 1926, when she was again admitted to the hospital. As on previous examination, the motor, sensory and reflex examination gave normal findings. She was nearly blind, and cooperation was very poor. Five days later, she suddenly became cyanotic; the blood pressure could not be read; the respirations were 40, and she died twelve hours later. At necropsy, there was a large hemorrhage in the left occipital lobe which was probably the immediate cause of death. In the interpeduncular space, a large mass of irregular outline was seen; its surface was covered with tiny cysts. The mass extended from the anterior surface of the pons to the optic chiasm on which it exerted pressure as well as on the tracts laterally. Within the anterior portion of the mass was included the infundibulum. On section, the tumor was seen to take its origin from the choroid plexus of the third ventricle.

DISCUSSION

DR. J. H. LLOYD: This case is interesting from several standpoints. It tends to confirm, as Dr. Russell says, the conclusions of Camus and Roussy in their experiments on dogs. Tumors at the base of the brain may cause hypophysial symptoms, even though the tumors are not of the hypophysis; and tumors of the hypophysis may cause symptoms that are not hypophysial. Such cases are of peculiar interest to the surgeon, because they may seriously mislead him. Dr. Grant and I presented a case recently to this society, in which a large tumor of the pituitary body extended as far back as the cerebellum, and yet caused few, if any, symptoms except the syndrome of Fröhlich.

A CASE SHOWING CONTRALATERAL ASSOCIATED MOVEMENTS. DR. H. H. HART.

The case I shall present is that of a boy, aged 14, who shows in addition to a general defect in intelligence a condition characterized by the persistence of automatic associated movements in any limb when corresponding purposeful and voluntary movements are executed in the other. This occurs particularly when the voluntary movements are of a more or less complicated nature — as in writing or opposition of the thumb to one finger after another but occurs also in less complicated movements such as the clenching of the fists and the flexion of the arms.

Clinical History.—Both the mother and the father are healthy, of apparently average intelligence, and there is no history of feeblemindedness in the family. The mother has had no miscarriage. The patient's birth was normal and he was a healthy infant. He suffered from none of the usual children's diseases. He showed early definite signs of delayed development. At the age of 1 year he was able to say "mama" and "papa." At the age of 3 he would call simple objects by their names but real formation of sentences did not develop until the age of from 6 to 7 years. As a child he never crept. It was not until he reached his second year that he was able to stand and by his third year only was he able to walk without support. To his parents he seemed definitely more awkward than a child of his own age. At this age he was first brought to the clinic because of the defective development. The record of this visit states that his face was aged in appearance and had also a typical adenoid character.

He was again brought to the clinic at the age of 14. He had had no serious illnesses in the interval of eleven years but had advanced only as far as the sixth grade in a parochial school. His brother, two years younger, is now two years ahead of him. When he appeared at school he was first noticed to hold objects in and to write with preference with the left hand. His father noticed that he picked objects up more easily with the left hand and threw a baseball always with that hand.

Examination.—The general skeletal growth is normal save for a marked cranial asymmetry and a tendency to the "Turmschadel" effect with sloping of the cranial bones toward the vertex. The teeth are very irregular and show some decay; the palate is extremely high and narrow; the pubic hair is scanty. The cranial nerves show no abnormalities. There is no sensory impairment. The tendon reflexes are somewhat exaggerated, particularly in the lower extremities. The patient uses the left hand more than the right in writing, tying his shoe laces and buttoning his clothes. The gait is somewhat mincing in character — is not awkward or ataxic but shows absence of the associated

movements of arm swinging. There is an increased muscular tonus in both upper and lower limbs.

When he is told to write with his left hand, movements of the fingers similar to the writing movements also occur in the right hand. He does not show mirror writing. Opposition of thumb to finger rapidly in either hand is followed by a similar but incomplete movement of the other hand. Clenching of either fist causes a complete clenching of the opposite one. When given more complicated combinations of voluntary movements, such as rubbing the abdomen with one hand and scratching the chest with the other, he fails to produce these two activities simultaneously but only alternately.

Inasmuch as the infant and child slowly overcome this tendency to bilateral synergism of the muscles through the acquisition of more complicated performances involving one limb only such as in writing, handling objects, etc., the presence of this phenomenon in this case can be regarded most probably as a sign of defective psychomotor development; it is met with frequently in conditions of idiocy, imbecility and high grades of mental retardation.

A case presenting similar persisting associated movements and mirror writing was shown to this society, in January, 1913, by Dr. Burr and Dr. Crow. In their case, the condition developed soon after birth in a child who gave a history of infantile palsy which cleared up and was not associated with an abnormal mental state. This patient, at the age of 27, had difficulty in any trade in which he could not use both hands at once.

Trophic Ulceration Following Transverse Myelitis of Meningitic Origin. Dr. Temple Fay.

A white man, aged 35, whose chief complaints were loss of sensation in the lower half of the body and recurrent ulceration of the legs, was admitted to the Episcopal Hospital, in February, 1918, with a middle ear condition which was diagnosed otitis media. At this time the patient developed pneumonia and tonsillitis, but made a good recovery. The condition showed evidence of recurrence and the patient became toxic. Paracentesis was done and the patient was discharged improved in March, 1918. Two days later he was admitted with symptoms of meningitis. Frequent spinal punctures were performed; during this time the patient was delirious, and had a septic type of temperature. A simple mastoid operation was performed, but no pus was found in the mastoid cells. Spinal puncture showed a turbid fluid with many pus cells and intracellular diplococci. Twelve days after admission, antimeningococcic serum was given intraspinally. The culture showed a pneumococcus. The patient was discharged one month after admission, with difficulty in walking and marked sensory disturbances in the lower extremities; he was referred to the outpatient department and has been under frequent observation for the last seven years. In 1923, he complained of spells in which everything blurred before his eyes. He had attacks of headache and vomiting. The attacks occurred at about three week intervals and were associated with extreme throbbing in the head, which required going to bed, and were usually relieved after one day or so of rest. Since the attack of meningitis, he has complained of loss of sensation in the lower limbs, especially the left leg, and there has been disturbance of sphincteric function with weakness of the bladder and complete loss of sexual power.

Examination.—Marked impairment of station; ataxia in the lower extremities; increase in reflexes; weakness, and loss of touch sense on the left up to the umbilicus, with impairment on the right, were shown at this time. Examina-

tion of the eyegrounds showed exudation in the nasal margin, which was thought to be congenital medullation of the nerve sheaths. There was no evidence of choking or pallor of the disks. The patient refused lumbar puncture.

Course.—In February, 1924, there developed ulcerations in the lower extremities. These improved under local treatment and completely healed in about two months. In March, 1924, there were decided ataxia of the lower extremities, trophic ulceration on the left ankle, loss of patellar reflexes and persistence of the bladder disturbance. The level of anesthesia had become definitely marked, as high as Poupart's ligament on each side. Some improvement was obtained under the administration of iodide and mercury, and it was felt that syphilis should be considered, although the Wassermann reaction of the blood was negative.

In January, 1925, the patient returned with a large ulcer and an herpetic eruption over the outer portion of the left leg. A large ulcer on the right ankle had been present for some time, but was improving.

In March, 1925, marked ulceration of the left knee occurred with great swelling. There was no improvement in the general condition. Loss of pain and touch sense in the lower extremities, as high as the umbilicus, was noted. Atrophy was not present and motor power was good. The reflexes were markedly increased in the Achilles and cremasteric arcs, the patellars being absent. Rectal and bladder disturbances were marked.

In September, 1925, the patient returned, having been at work continuously. He complained only of disturbance of the sphincter control.

Feb. 17, 1926, the man was seen after a period of improvement in which the ulcerations had completely healed and he had worked as night watchman and produce distributor. During the last week, however, he has had a return of the ulcerations which are confined to the lower extremities, especially to the left leg where there is a large ulcer over the patellar region, another of the second toe and one at the ankle. A small ulcerating area is present on the left hip. On the right there are several deep, clear-cut ulcerating areas without signs of local inflammation. The sensory level at this time is as high as the ninth dorsal segment on both sides, with complete loss of pain, temperature, vibration, sense of position and passive movement senses. Tactile sensation is greatly impaired, and he only occasionally recognizes touch in the lower extremities, especially on the right. The motor power of the lower limbs is somewhat impaired; there is a distinct tendency toward spasticity with increase in Achilles reflexes, reactions of defense, involuntary jerkings, bilateral clonus and Babinski signs. There is marked atrophy of the left leg.

Examination of the cranial nerves gives entirely negative results, except for a slight nystagmus on looking to the right and impaired hearing of the left ear which was the site of the old otitis media. The pupils are regular and equal, and respond to light and in accommodation. There is no ataxia of the upper extremities, but the reflexes of the upper extremities are increased. The Romberg sign is marked. The abdominal reflexes are lost. What appears to be an exaggerated patellar reflex is obtained on striking the patellar tendon. This, however, may be a reaction of defense produced by the usual reflex stimulation. It is impossible to obtain the left patellar reflex at this time, because of the extensive ulceration. There are many marked fibrillary tremors confined to the pectoral group on the right side. Spasmodic myoclonus of the abdominal muscles is present on the left.

The symptoms of transverse myelitis are definite to the level of the ninth dorsal segment. However, the increase in reflexes of the upper extremity,

the slight nystagmus and fibrillary tremors indicate involvement in other regions of the nervous system. The condition strikingly simulates multiple sclerosis and is presented before the society as an unusual case of recurrent ulceration, probably trophic in character, occurring periodically in the area of anesthesia. There is undoubtedly still present an irritative factor, as shown by the fibrillary tremors and recurrent ulceration, which is myelitic in type, not only confined to the dorsal roots but involving the gray matter as well.

Occlusion of Anterior Tibial Artery. Dr. George Wilson.

This patient is presented because pain was a prominent symptom in his illness and, while the condition is not neurologic in its nature, certain symptoms in the case make it of neurologic interest. A man, aged 38, married but without children, had an unimportant past history with the exception of three attacks of gonorrhea. He was in good health until the evening of Jan. 7, 1926, when after dinner in an Italian restaurant he became acutely ill with vomiting and diarrhea. These symptoms persisted for a few hours and then ceased. He went to bed, but about midnight was awakened with an agonizing cramp in the left leg, radiating from the ankle to the knee. The pain was greatest in two places: a point about 6 inches (15 cm.) above the ankle on the anterior aspect, and in the calf a few inches below the knee. The pain persisted throughout that night. The man remained in bed the following day and took a short walk in the evening, but the exercise brought a return of the pain in the leg. For the next four or five days, he had no pain as long as he was at rest, but a dull ache or a cramp appeared in the calf of the leg if he walked any distance.

On the fourth day of the illness, after taking a hot bath, he noticed that the left foot was as white as marble, whereas the right was of ordinary color; the left foot and the lower third of the left leg was cold to the touch and covered with a clammy perspiration. I saw the patient for the first time five days after the onset.

Examination.—The routine neurologic examination gave negative results with the exception of an area of hypesthesia along the outer border of the left foot. The lungs, heart and abdomen showed no evidence of disease, and the blood pressure was within the normal limits. The left foot was cool and covered with perspiration. Pulsation of the dorsalis pedis artery in the left foot was absent. A point of tenderness was present at about the middle of the calf; this was deepseated and seemed to vary in intensity from day to day. The examinations of the blood and urine were normal. The prostatic secretion was practically all pus and the prostate itself was soft and boggy.

Clinical Course and Outcome.—The man was kept in bed and dry heat was applied to the foot and leg. He improved steadily so that at the end of about two weeks he was practically well. Pulsation has returned very slightly in the dorsalis pedis artery.

The intense pain in the case was probably due to involvement of the periarterial sympathetic. The etiologic factor was most likely food poisoning plus a chronic prostatitis.

The Primary Afferent Centers of the Brain Stem. Dr. Walter Freeman.

On two previous occasions I have addressed this society on certain details of the anatomy of the brain stem, pointing out that more than one nerve contributed to a certain tract or nucleus. In the case of the radix mesencephalica

trigemini I suggested that the large cells lying close to the aqueduct relayed muscular impressions not only from the muscles of mastication, but also from the extra-ocular muscles. In the second paper I presented evidence to show that the radix spinalis trigemini carried fibers not only from the fifth but also from the seventh, ninth and tenth nerves, and that the fifth nerve during the course of development had, to a considerable degree, usurped the field and function of these other nerves.

On this occasion, I wish to touch on these points and to mention others of similar nature, and to bring them all into harmony with the doctrine of nerve components. This doctrine states that the nerve axis is divided longitudinally into four columns that extend laterally from the median septum. These divisions relay respectively somatic efferent, visceral efferent, visceral afferent and somatic afferent impulses. These columns are seen with greatest distinctness in the medulla oblongata of the dogfish in which they are least complicated by extraneous factors. The arrangement is somewhat more complex in the human medulla oblongata but the four columns are quite discernible. I shall limit myself to the afferent divisions.

The spinal cord has been studied from the point of view of the column rather than from the point of view of the individual nerves. The individual nerves are too much alike to warrant special study. It is only recently, however, that the same method of study has been applied to the brain stem. The nerves show such marked differences that for a long time they were considered as entities. But in spite of the obvious differences presenting, there still remain features in common. It is these that I wish to stress, taking the spinal cord as a pattern.

A typical spinal nerve, for example, conveys motor impulses to a certain number of voluntary muscles and to a certain stretch of involuntary muscle through sympathetic connections. It conveys impulses of cutaneous sensibility from a certain area of skin, proprioceptive impulses from certain muscles, joints, etc., and visceral impulses from a certain portion of the alimentary canal. The "mixed" nerves of the brain stem seem to fulfil these requirements. The cutaneous field of the trigeminal nerve is well known. This nerve also innervates the mucosa of the nose and mouth (interoceptive sensibility), and it carries deep sensibility from the muscles of mastication, from the periosteum of the facial and cranial bones and from the dura. The facial nerve innervates the skin in the region of the ear, perhaps a small area of mucous membrane in the region of the fauces and certainly the anterior taste buds (special interoceptive sensibility), and it carries proprioceptive impulses from the muscles of expression. The glossopharyngeal nerve has a few cutaneous filaments appearing in the region of the ear, it gives fibers to the mucosa of the pharynx and to the posterior taste buds, while it relays muscle sensibility from the muscles it innervates (superior constrictor of the pharynx and possibly others). The pneumogastric nerve also carries exteroceptive sensation from the region of the ear, interoceptive sensation from the respiratory and alimentary tracts, and proprioceptive sensation from the muscles of the pharynx and possibly of the larynx. Some of the details of this partition of innervation have not yet been worked out satisfactorily, but I believe that the principle stands. A glance at the drawings of the cutaneous branches of these nerves in the fish, and at the probable cutaneous fields in man may be taken as an indication for the rest.

Returning now to the spinal cord as a model, and dividing it according to the doctrine of nerve components so ably advanced by Johnston, Herrick, Kappers and others, it will be seen that some further division and recom-

bination is necessary. Exteroceptive sensations are carried to two centers, one of which, the dorsal cornu, is strictly segmental, and the other, the dorsal nuclei of Goll and Burdach, represented in the cord by the dorsal funiculi. The first relays simple impressions of touch, pain and temperature, while the second relays the more highly elaborated modulations of sensibility that might be called discriminative. Thus there are in the cord two areas of exteroceptive import, the dorsal cornu and the dorsal column.

The interoceptive column, or visceral afferent, is located in the pars intermedia of the spinal cord.

The proprioceptive column also consists of two divisions. Simple impulses for muscle tone and posture that never reach consciousness are transmitted by way of Clark's column to the cerebellar vermis. Those underlying the more complicated adjustments to external objects, those that subserve stereognostic perception, run with the exteroceptive discriminative impulses in the dorsal columns of the spinal cord to the nuclei of Goll and Burdach. The exteroceptive and proprioceptive impulses are both of the somatic afferent type and have so been grouped by some of the investigators. Some additional information may, however, be gained by their separation.

Applying these data to the medulla oblongata and pons is not altogether easy. One component of one medullary nerve is exaggerated and another nearly suppressed, whereas the relationship differs in another segment. Moreover, as higher levels are approached the architectural pattern is complicated by secondary centers and tracts and by an increasing number of new and suprasegmental structures.

The primitive exteroceptive column represented by the dorsal cornu of the spinal cord is continued into the brain stem as the substantia gelatinosa rolandi of the fifth nerve. It receives filaments not only from the fifth but also probably from the seventh, ninth and tenth nerves.

The exteroceptive discriminative column is represented by the upper portions of the nucleus cuneatus into which some of the lower vagus fibers seem to run, and by the nucleus sensibilis trigemini. Between these two nuclei, and lying in the same relative position with regard to the corpus restiforme, are two small homologous nuclei that may prove to be the reception nuclei for exteroceptive discriminative and proprioceptive cognitive impressions of the seventh and ninth nerves. I have not yet had the opportunity of determining whether these small nuclei, like the larger ones, undergo atrophy in cases of thalamic destruction.

The interoceptive column is represented by the nuclei that accompany the tractus solitarius. The tractus solitarius is composed of primary afferent fibers from the ninth and tenth nerves, but entering fibers running to the same column can also be seen at the levels of the fifth and seventh nerves. The column can be traced from the middle of the pons directly into the pars intermedia of the spinal cord. This nucleus relays impressions of simple visceral sensibility rather than those of taste. It is developed only in air-breathing animals; it is strong in birds which have scarcely any taste buds; and absent from fishes that have these in extraordinary numbers; the nucleus is largest at the level of the vagus nerve, a nerve that in man supplies scarcely any taste buds. The gustatory nuclei are recognizable at the levels of entry of the seventh and ninth nerves as small clear nuclei lying close to the nucleus of the fasciculus solitarius.

The proprioceptive column represented in the cord by Clarke's nucleus lies between the exteroceptive and interoceptive columns. In the medulla oblongata

it undergoes remarkable expansion as the proprioceptive fibers of the eighth nerve enter its composition. The descending tract of the eighth nerve with its accompanying nucleus can be traced into the position of the column of Clarke in the spinal cord, where it lies slightly lateral to the caudal extension of the fasciculus solitarius. This center receives fibers not only from the eighth nerve, but also probably from the other nerves of the medulla. The tract becomes larger below the entry of the vagus roots; entering fibers can be seen joining with the rest of the descending fibers, and tearing out the afferent roots of the lower nerves leads to some degeneration in the root. The secondary pathway from this center, as from the column of Clarke, leads to the vermis cerebelli.

The long caudal extension of the root is probably to be explained by the concentration of proprioceptive function of vestibular equilibration in one nerve instead of in three as in the fish. The cells of origin of the secondary pathway are laid down in primitive fashion, segmentally, and do not change their positions. Therefore, to connect with them, the primary axons, even though entering by a different nerve, must pursue a path of some extent before coming into relation with the cells of origin of the secondary pathway.

The cognitive function of the proprioceptive portion of the eighth nerve is carried out by the acoustic apparatus. The auditory nuclei seem to resemble the proprioceptive cognitive nuclei of other nerves, although there is great specialization. The cells are of the same general order, their axons run in rather close proximity to those in the median fillet, i. e., the lateral fillet, and they terminate, at least in part, in a division of the thalamus, the median geniculate body. The overgrowth of this portion of the proprioceptive column has brought about a mushroom expansion of the tegmentum of the medulla oblongata which spreads over the confines of the restiform body and lateral angle of the fourth ventricle.

Considered in this light, the eighth nerve appears to be a highly specialized portion of the seventh nerve. Indeed the ganglia of the two nerves arise from a common anlage in the neural crest.

The cephalic prolongation of the proprioceptive column seems to be the radix mesencephalica trigemini with its attendant large cells. These cells, as Johnston has shown, are homologous with the large cells in the dorsolateral portion of the spinal cord of amphioxus, an animal that has no spinal ganglia. They probably relay muscle sensibility. These large cells are not homologous with those of Clarke's column since they are primary neurons, but the origin of the secondary pathway has not been described. There are reasons for believing that the large cells of the nucleus mesencephalica trigemini conduct impressions of muscular activity not only from the muscles of mastication but also from the extra-ocular muscles. The cells are numerous at the level of the third nucleus; the nerve has no root ganglion; Golgi saw some processes of these cells joining the fibers of the trochlear nerve; the nucleus is not destroyed by section of the root of the fifth nerve. In some experiments on cats, exenteration of the orbit produced sensible diminution in the number of cells on the side of operation at the level of the oculomotor nucleus. In a case of ophthalmoplegia the cells in the cephalic portion of the nucleus were greatly diminished in number. It would seem, therefore, that these cells in the upper portion of the root relayed impressions of muscular activity from the extra-ocular muscles.

The primary afferent centers of the brain stem may now be grouped into the following scheme: Exteroceptive, common cutaneous sensibility is relayed by the nucleus of the radix spinalis trigemini, the continuation of the substantia gelatinosa rolandi of the spinal cord. Exteroceptive discriminative and

proprioceptive cognitive sensibilities are relayed by the dorsal funicular nuclei of Goll and Burdach, by the main sensory nucleus of the fifth nerve, and probably by two small nuclei in this same column receiving fibers from the seventh and ninth nerves. Finally, the fibers subserving the special proprioceptive cognitive function of hearing find their relay station in the nucleus ventralis nervi acustici and in the tuberculum acusticum, specialized portions of the proprioceptive cognitive system. Interoceptive nuclei lie in a chain extending from the pons caudad directly into the pars intermedia of the spinal cord. Two small nuclei at the levels of entry of the seventh and ninth nerves probably relay gustatory impressions. Proprioceptive impulses underlying muscle tonus and coordination coming from the lower nerves of the brain stem, find their relay stations in the nucleus of the descending tract of the eighth nerve which is traceable directly into Clarke's column in the spinal cord. Similar impulses from the fifth nerve, and probably also from the oculomotor nerves, are relayed by the nucleus mesencephalica trigemini.

The inductive method, the application of the doctrine of nerve components, to the study of the primary afferent centers in the brain stem, leads to the identification of many structures in terms of their homologues in the spinal cord. It also shows that the same nucleus or center relays impulses from more than one nerve, that there are no *viae privatae* among the primary afferent centers.

DISCUSSION

Dr. J. H. Lloyd: Do I understand from Dr. Freeman that morphologists agree that the seventh nerve contains sensory fibers? This question has been debated among neurologists and is of clinical interest. Cases of herpes occur in which the eruption is limited to a small area in front of and behind the ear; it is always accompanied by paralysis of the seventh nerve. Ramsay Hunt collected a number of such cases, which are doubtless due to a herpetic lesion in the geniculate ganglion, and he drew the conclusion that the seventh nerve contains sensory fibers. I have always thought that he may be right.

Dr. Walter Freeman: The question of the cutaneous impulses carried by the seventh nerve has been fought over for twenty years. In 1907 Ramsay Hunt published his papers on the syndrome of the geniculate ganglion. Cutaneous fibers of the facial nerve exist in many lower animals. They are important in some of the lower fishes, some amphibia and reptiles; they have been described in detail by Rinehart in the albino mouse. For fifty years or more anatomists have recognized the presence of cutaneous filaments in the facial nerve, and again as recently as 1918 Baudouin published a detailed study of these fibers. The syndrome of the geniculate ganglion, comprising an eruption of vesicles in the ear, of facial paralysis and of loss of the sense of taste on the anterior part of the tongue is a fairly definite syndrome. Dejerine describes the condition in his textbook. A number of cases were reported in the *Revue neurologique* in 1921.

I would again like to refer to a patient in Dr. Frazier's service whom I had the privilege of observing. I believe this is the only case of a study of the cutaneous sensory field by means of the method of residual innervation. This patient underwent trigeminal neurectomy for trifacial neuralgia, and a few days after the operation developed facial paralysis. When the area of anesthesia was charted it was found to include the whole of the external surface of the auricle, the lobe and the anterior wall of the external auditory canal. The concha was sensitive. After the facial paralysis had cleared up, the area of anesthesia included only the root of the auricle.

Book Reviews

NOUVEAU TRAITÉ DE MÉDECINE. PATHOLOGIE DU CERVEAU ET DU CERVELET. VOLUME XIX. Edited by G. H. ROGER, FERNAND WIDAL and P. J. TEISSIER. Price, 80 francs. Pp. 1,016. Paris: Masson et Cie., 1925.

It can be taken for granted that medical periodicals reflect the current scientific thought, but textbooks reflect the more mature consideration of the trends of our sciences. This is very interestingly demonstrated in this the latest book on diseases of the cerebrum and cerebellum, which is the nineteenth volume of a new system of medicine edited by G. H. Roger, F. Widal and P. J. Teissier. Two previous volumes related to neurology have already appeared, volume 8, which considers the endocrine disorders, and volume 18, which discusses the symptomatology of some cerebral disorders. Three more volumes are still to appear: volume 20 on diseases of the bulb, cranial nerves, meninges and spinal cord; volume 21 on neuralgias, the sympathetic system and the neuroses; volume 22 on muscular affections, dystrophies and allied topics.

This volume contains a series of monographs by various authors who have been exceedingly well chosen. The opening discussion by Klippel and Monier-Vinard is on the pyramidal syndrome. The second is by Roussy and Cornil on cerebral hemianesthesia. It is brief but quite adequate and on a topic to which Roussy has contributed very largely; then in order, contributions on hemianopia, jacksonian epilepsy, the topography of the cranium and cortical syndromes. They are along conventional lines, but the chapter on the topography of the cranium is unusual and well illustrated, and a subject not often discussed in textbooks.

It is however, the next article on the subcortical syndromes by Klippel and Lhermitte which is worthy of especial comment, for here for the first time in a textbook there is an adequate presentation and classification of striatal diseases. The subheadings are as follows: the syndromes of the corpus striatum; progressive lenticular degeneration (Wilson's disease); pseudo-sclerosis; the syndrome of Westphal-Strümpell; progressive lenticular dystonia; parkinsonian syndrome; the thalamic syndrome; athetosis; the syndrome of the callosum and the ventricular syndrome. Under the foregoing there are of course subclassifications, for example, in the syndrome of the corpus striatum there is the pallidal syndrome, lesions of the corpus striatum both unilateral and bilateral, and hepatic striatal degenerations; while under the thalamic syndrome the well known Dejerine-Roussy syndrome is given a prominent heading. The discussion of the diseases of the callosum is quite unusual, for this part of the brain has obtained perhaps the least recognition in text-books. The same can be said of the ventricular syndrome.

The presentation of the foregoing material is along modern lines and in the discussion of the corpus striatum an attempt is made at localization of function. This is quite opposite to the view recently expressed by Kinnier-Wilson in his Croonian lectures. However, knowledge of the functions of the striatum and the basal ganglia will, in all probability, remain a mystery for a long time to come.

The next chapter on traumatism of the brain by Marchand is excellent. Infections properly receive a separate chapter, and in this encephalitis and

abscess of the brain are discussed. Vascular disturbances next receive attention. It is interesting to note that anemia and congestion of the brain are still discussed under separate headings as they should be. In this classification aneurisms, thromboses and changes occurring in senility are given adequate presentation. Pseudobulbar paralysis also receives a separate chapter although this might have been placed with diseases of the striate body. Then follow chapters on tumors of the brain, cerebral syphilis and general paralysis, and encephalopathies.

The second large subdivision of the book is on the diseases of the cerebellum and syndromes of the labyrinth. This part, which occupies about 250 pages, is mostly written by André Thomas, the labyrinthian syndrome being discussed by Hautant, the latter only taking about twenty pages. Too much praise cannot be given for this chapter. André Thomas' views of the cerebellum are well known. In fact, what is presented here is similar in outline to his monograph on cerebellar diseases which appeared several years ago. He has, however, brought it up to date. It is, perhaps, the best short presentation of the cerebellum and its diseases to be found anywhere. It is interesting that he admits that there is cerebellar localization which he was inclined to doubt in his monograph. Another interesting fact is that Friedreich's disease is included in cerebellar diseases. Why this has not been done before is a mystery.

The book is exceedingly well illustrated. There are a number of excellent colored illustrations but the outstanding feature is the use by André Thomas of moving picture illustrations. Perhaps cerebellar disease more than any other locomotor disturbance lends itself better to moving picture illustrations and the author has taken full advantage of it. It is well to point out here that the first use of moving picture illustrations in textbook articles was by an American, who used it in illustrations of all sort of gaits and symptoms in nervous disorders.

Altogether this is an unusually well conceived volume which, while it presents nothing startlingly new, nevertheless is a striking illustration of the tendency of modern neurologic thought, especially of the younger French neurologists.

INTERNATIONAL CLINICS. Edited by HENRY W. CATTELL, A.M., M.D. Vol. I. Series 36. Pp. 304. Philadelphia: J. B. Lippincott Company, March, 1926.

The present volume is not of great interest to neurologists. There is an interesting paper by Professor Kraepelin on "The Development of Psychiatrical Research," it being a reprint of an address delivered by him in Chicago. In another article by Professor Plaut the malarial treatment of syphilis is taken up, but the discussion is not at all adequate. There is also a report of a case of paraplegia in Hodgkin's disease with a collection of literature.